

## Refine Search

### Search Results -

Terms	Documents
L9 and hydroxylphenyl	28

Database:

US Pre-Grant Publication Full-Text Database  
 US Patents Full-Text Database  
 US OCR Full-Text Database  
 EPO Abstracts Database  
 JPO Abstracts Database  
 Derwent World Patents Index  
 IBM Technical Disclosure Bulletins

Search:

L10





### Search History

DATE: Monday, January 26, 2004    [Printable Copy](#)    [Create Case](#)

Set Name Query

side by side

Hit Count Set Name

result set

DB=USPT; PLUR=YES; OP=OR

<u>L10</u>	L9 and hydroxylphenyl	28	<u>L10</u>
<u>L9</u>	l2 and L8	164	<u>L9</u>
<u>L8</u>	c-jun inhibition	103733	<u>L8</u>
<u>L7</u>	L6 and l4	15	<u>L7</u>
<u>L6</u>	c-jun activation adj2 inhibition	2036	<u>L6</u>
<u>L5</u>	L4 and inhibit c-jun	1002	<u>L5</u>
<u>L4</u>	L3 and hydroxylphenyl	28	<u>L4</u>
<u>L3</u>	L2 and l1	155	<u>L3</u>
<u>L2</u>	dimethoxyquinazoline	268	<u>L2</u>
<u>L1</u>	inhibit c-jun activation	370075	<u>L1</u>

END OF SEARCH HISTORY

## Refine Search

### Search Results -

Terms	Documents
L3 and hydroxylphenyl	18

Database:

US Pre-Grant Publication Full-Text Database  
US Patents Full-Text Database  
US OCR Full-Text Database  
EPO Abstracts Database  
JPO Abstracts Database  
Derwent World Patents Index  
IBM Technical Disclosure Bulletins

Search:

L5

Refine Search

Recall Text

Clear

Interrupt

### Search History

DATE: Monday, January 26, 2004 [Printable Copy](#) [Create Case](#)

#### Set Name Query

side by side

DB=USPT; PLUR=YES; OP=OR

L5 L3 and hydroxylphenylL4 hydroxylphenyl and L3L3 L2 and dimethoxyL2 quinazolineL1 bromo-hydroxylphenyl-amino-dimethoxyquinazoline

#### Hit Count Set Name

result set

18 L50 L41056 L34397 L20 L1

END OF SEARCH HISTORY

## Hit List

Clear	Generate Collection	Print	Fwd Refs	Bkwd Refs
Generate OACS				

Search Results - Record(s) 1 through 10 of 18 returned.

☐ 1. Document ID: US 6638939 B2

L5: Entry 1 of 18

File: USPT

Oct 28, 2003

US-PAT-NO: 6638939

DOCUMENT-IDENTIFIER: US 6638939 B2

TITLE: 6,7-dimethoxyquinazolines and therapeutic use thereof

DATE-ISSUED: October 28, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Liu; Xing-Ping	Minneapolis	MN		
Narla; Rama Krishna	St. Paul	MN		

US-CL-CURRENT: 514/266.4; 544/293

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequence	Attachment	Claims	KIMC	Draw De
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☐ 2. Document ID: US 6552027 B2

L5: Entry 2 of 18

File: USPT

Apr 22, 2003

US-PAT-NO: 6552027

DOCUMENT-IDENTIFIER: US 6552027 B2

TITLE: Quinazolines for treating brain tumor

DATE-ISSUED: April 22, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Narla; Rama Krishna	St. Paul	MN		
Liu; Xing-Ping	Minneapolis	MN		

US-CL-CURRENT: 514/266.4

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWIC	Draw D
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☐ 3. Document ID: US 6495556 B2

L5: Entry 3 of 18

File: USPT

Dec 17, 2002

US-PAT-NO: 6495556

DOCUMENT-IDENTIFIER: US 6495556 B2

**\*\* See image for Certificate of Correction \*\***TITLE: Dimethoxy quinazolines for treating diabetes

DATE-ISSUED: December 17, 2002

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Leak	MN		
Sudbeck; Elise A.	St. Paul	MN		
Cetkovic; Marina	Maplewood	MN		
Malaviya; Ravi	Shoreview	MN		
Liu; Xing-Ping	Minneapolis	MN		

US-CL-CURRENT: 514/266.4

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWIC	Draw D
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☐ 4. Document ID: US 6469013 B2

L5: Entry 4 of 18

File: USPT

Oct 22, 2002

US-PAT-NO: 6469013

DOCUMENT-IDENTIFIER: US 6469013 B2

**\*\* See image for Certificate of Correction \*\***

TITLE: Therapeutic compounds

DATE-ISSUED: October 22, 2002

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Sudbeck; Elise A.	St. Paul	MN		
Cetkovic; Marina	Maplewood	MN		
Malaviya; Ravi	Shoreview	MN		
Liu; Xing-Ping	Minneapolis	MN		

US-CL-CURRENT: 514/266.3; 514/266.4

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWIC	Draw D
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☐ 5. Document ID: US 6452005 B1

L5: Entry 5 of 18

File: USPT

Sep 17, 2002

US-PAT-NO: 6452005

DOCUMENT-IDENTIFIER: US 6452005 B1

**\*\* See image for Certificate of Correction \*\***

TITLE: JAK-3 inhibitors for treating allergic disorders

DATE-ISSUED: September 17, 2002

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Malaviya; Ravi	Shoreview	MN		
Sudbeck; Elise A.	St. Paul	MN		

US-CL-CURRENT: 544/293

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWIC	Draw De
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☐ 6. Document ID: US 6410545 B1

L5: Entry 6 of 18

File: USPT

Jun 25, 2002

US-PAT-NO: 6410545

DOCUMENT-IDENTIFIER: US 6410545 B1

**\*\* See image for Certificate of Correction \*\***TITLE: Lipid lowering quinazoline dietary supplement composition

DATE-ISSUED: June 25, 2002

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Trieu; Vuong N.	Roseville	MN		
Liu; Xing-Ping	Minneapolis	MN		

US-CL-CURRENT: 514/266.1; 514/266.3

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWIC	Draw De
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☐ 7. Document ID: US 6358962 B2

L5: Entry 7 of 18

File: USPT

Mar 19, 2002

US-PAT-NO: 6358962

DOCUMENT-IDENTIFIER: US 6358962 B2

TITLE: 6,7-Dimethoxyquinazolines and therapeutic use thereof

DATE-ISSUED: March 19, 2002

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Liu; Xing-Ping	Minneapolis	MN		
Narla; Rama Krishna	St. Paul	MN		

US-CL-CURRENT: 514/266.4; 544/283, 544/293

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWIC	Draw D
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☐ 8. Document ID: US 6355645 B2

L5: Entry 8 of 18

File: USPT

Mar 12, 2002

US-PAT-NO: 6355645

DOCUMENT-IDENTIFIER: US 6355645 B2

TITLE: Lipid-lowering quinazoline derivative

DATE-ISSUED: March 12, 2002

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Trieu; Vuong N.	Roseville	MN		
Liu; Xing-Ping	Minneapolis	MN		

US-CL-CURRENT: 514/266.1; 514/266.3, 514/266.4, 544/283, 544/286

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWIC	Draw D
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☐ 9. Document ID: US 6326373 B1

L5: Entry 9 of 18

File: USPT

Dec 4, 2001

US-PAT-NO: 6326373

DOCUMENT-IDENTIFIER: US 6326373 B1

**\*\* See image for Certificate of Correction \*\***

TITLE: JAK-3 inhibitors for treating allergic disorders

DATE-ISSUED: December 4, 2001

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Malavia; Ravi	Shoreview	MN		
Sudbeck; Elise A.	St. Paul	MN		

US-CL-CURRENT: 514/266.1; 514/266.3, 514/266.4

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	RWMC	Draw De
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☐ 10. Document ID: US 6316454 B1

L5: Entry 10 of 18

File: USPT

Nov 13, 2001

US-PAT-NO: 6316454

DOCUMENT-IDENTIFIER: US 6316454 B1

TITLE: 6,7-Dimethoxy-4-anilinoquinazolines

DATE-ISSUED: November 13, 2001

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Narla; Rama Krishna	St. Paul	MN		
Liu; Xing-Ping	Minneapolis	MN		

US-CL-CURRENT: 514/266.3; 514/266.4, 544/293

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	RWMC	Draw De
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Clear	Generate Collection	Print	Fwd Refs	Bkwd Refs	Generate OACS
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Terms	Documents
L3 and hydroxylphenyl	18

Display Format:  [Previous Page](#)[Next Page](#)[Go to Doc#](#)

## Hit List

Clear	Generate Collection	Print	Fwd Refs	Bkwd Refs
Generate OACS				

**Search Results - Record(s) 1 through 10 of 18 returned.**

☐ 1. Document ID: US 6638939 B2

L5: Entry 1 of 18

File: USPT

Oct 28, 2003

US-PAT-NO: 6638939

DOCUMENT-IDENTIFIER: US 6638939 B2

TITLE: 6,7-dimethoxyquinazolines and therapeutic use thereof

DATE-ISSUED: October 28, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Liu; Xing-Ping	Minneapolis	MN		
Narla; Rama Krishna	St. Paul	MN		

US-CL-CURRENT: 514/266.4; 544/293

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KOMC	Draw De
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☐ 2. Document ID: US 6552027 B2

L5: Entry 2 of 18

File: USPT

Apr 22, 2003

US-PAT-NO: 6552027

DOCUMENT-IDENTIFIER: US 6552027 B2

TITLE: Quinazolines for treating brain tumor

DATE-ISSUED: April 22, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Narla; Rama Krishna	St. Paul	MN		
Liu; Xing-Ping	Minneapolis	MN		

US-CL-CURRENT: 514/266.4



Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWIC	Drawings
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☐ 3. Document ID: US 6495556 B2

L5: Entry 3 of 18

File: USPT

Dec 17, 2002

US-PAT-NO: 6495556

DOCUMENT-IDENTIFIER: US 6495556 B2

**\*\* See image for Certificate of Correction \*\***TITLE: Dimethoxy quinazolines for treating diabetes

DATE-ISSUED: December 17, 2002

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Sudbeck; Elise A.	St. Paul	MN		
Cetkovic; Marina	Maplewood	MN		
Malaviya; Ravi	Shoreview	MN		
Liu; Xing-Ping	Minneapolis	MN		

US-CL-CURRENT: 514/266.4

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWIC	Drawings
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☐ 4. Document ID: US 6469013 B2

L5: Entry 4 of 18

File: USPT

Oct 22, 2002

US-PAT-NO: 6469013

DOCUMENT-IDENTIFIER: US 6469013 B2

**\*\* See image for Certificate of Correction \*\***

TITLE: Therapeutic compounds

DATE-ISSUED: October 22, 2002

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Sudbeck; Elise A.	St. Paul	MN		
Cetkovic; Marina	Maplewood	MN		
Malaviya; Ravi	Shoreview	MN		
Liu; Xing-Ping	Minneapolis	MN		

US-CL-CURRENT: 514/266.3; 514/266.4

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWIC	Drawings
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☐ 5. Document ID: US 6452005 B1

L5: Entry 5 of 18

File: USPT

Sep 17, 2002

US-PAT-NO: 6452005

DOCUMENT-IDENTIFIER: US 6452005 B1

**\*\* See image for Certificate of Correction \*\***

TITLE: JAK-3 inhibitors for treating allergic disorders

DATE-ISSUED: September 17, 2002

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Malaviya; Ravi	Shoreview	MN		
Sudbeck; Elise A.	St. Paul	MN		

US-CL-CURRENT: 544/293

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWIC	Draw. De
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☐ 6. Document ID: US 6410545 B1

L5: Entry 6 of 18

File: USPT

Jun 25, 2002

US-PAT-NO: 6410545

DOCUMENT-IDENTIFIER: US 6410545 B1

**\*\* See image for Certificate of Correction \*\***TITLE: Lipid lowering quinazoline dietary supplement composition

DATE-ISSUED: June 25, 2002

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Trieu; Vuong N.	Roseville	MN		
Liu; Xing-Ping	Minneapolis	MN		

US-CL-CURRENT: 514/266.1; 514/266.3

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWIC	Draw. De
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☐ 7. Document ID: US 6358962 B2

L5: Entry 7 of 18

File: USPT

Mar 19, 2002

US-PAT-NO: 6358962

DOCUMENT-IDENTIFIER: US 6358962 B2

TITLE: 6,7-Dimethoxyquinazolines and therapeutic use thereof

DATE-ISSUED: March 19, 2002

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Liu; Xing-Ping	Minneapolis	MN		
Narla; Rama Krishna	St. Paul	MN		

US-CL-CURRENT: 514/266.4; 544/283, 544/293

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KVMC	Draw De
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☐ 8. Document ID: US 6355645 B2

L5: Entry 8 of 18

File: USPT

Mar 12, 2002

US-PAT-NO: 6355645

DOCUMENT-IDENTIFIER: US 6355645 B2

TITLE: Lipid-lowering quinazoline derivative

DATE-ISSUED: March 12, 2002

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Trieu; Vuong N.	Roseville	MN		
Liu; Xing-Ping	Minneapolis	MN		

US-CL-CURRENT: 514/266.1; 514/266.3, 514/266.4, 544/283, 544/286

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KVMC	Draw De
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☐ 9. Document ID: US 6326373 B1

L5: Entry 9 of 18

File: USPT

Dec 4, 2001

US-PAT-NO: 6326373

DOCUMENT-IDENTIFIER: US 6326373 B1

**\*\* See image for Certificate of Correction \*\***

TITLE: JAK-3 inhibitors for treating allergic disorders

DATE-ISSUED: December 4, 2001

## INVENTOR-INFORMATION:

h e b b g e e e f e ef b e

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Malavia; Ravi	Shoreview	MN		
Sudbeck; Elise A.	St. Paul	MN		

US-CL-CURRENT: 514/266.1; 514/266.3, 514/266.4

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	RWC	Draw D
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☐ 10. Document ID: US 6316454 B1

L5: Entry 10 of 18

File: USPT

Nov 13, 2001

US-PAT-NO: 6316454

DOCUMENT-IDENTIFIER: US 6316454 B1

TITLE: 6,7-Dimethoxy-4-anilinoquinazolines

DATE-ISSUED: November 13, 2001

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Narla; Rama Krishna	St. Paul	MN		
Liu; Xing-Ping	Minneapolis	MN		

US-CL-CURRENT: 514/266.3; 514/266.4, 544/293

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	RWC	Draw D
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Clear	Generate Collection	Print	Fwd Refs	Bkwd Refs	Generate OACS
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Terms	Documents
L3 and hydroxylphenyl	18

Display Format:  [Previous Page](#)[Next Page](#)[Go to Doc#](#)

## Hit List

Clear	Generate Collection	Print	Fwd Refs	Bkwd Refs
Generate OACS				

Search Results - Record(s) 1 through 10 of 18 returned.

☐ 1. Document ID: US 6638939 B2

L5: Entry 1 of 18

File: USPT

Oct 28, 2003

US-PAT-NO: 6638939

DOCUMENT-IDENTIFIER: US 6638939 B2

TITLE: 6,7-dimethoxyquinazolines and therapeutic use thereof

DATE-ISSUED: October 28, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Liu; Xing-Ping	Minneapolis	MN		
Narla; Rama Krishna	St. Paul	MN		

US-CL-CURRENT: 514/266.4; 544/293

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequence	Attachment	Claims	KIMC	Draw. Dg
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☐ 2. Document ID: US 6552027 B2

L5: Entry 2 of 18

File: USPT

Apr 22, 2003

US-PAT-NO: 6552027

DOCUMENT-IDENTIFIER: US 6552027 B2

TITLE: Quinazolines for treating brain tumor

DATE-ISSUED: April 22, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Narla; Rama Krishna	St. Paul	MN		
Liu; Xing-Ping	Minneapolis	MN		

US-CL-CURRENT: 514/266.4

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWIC	Draw. De
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☐ 3. Document ID: US 6495556 B2

L5: Entry 3 of 18

File: USPT

Dec 17, 2002

US-PAT-NO: 6495556

DOCUMENT-IDENTIFIER: US 6495556 B2

**\*\* See image for Certificate of Correction \*\***TITLE: Dimethoxy quinazolines for treating diabetes

DATE-ISSUED: December 17, 2002

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Sudbeck; Elise A.	St. Paul	MN		
Cetkovic; Marina	Maplewood	MN		
Malaviya; Ravi	Shoreview	MN		
Liu; Xing-Ping	Minneapolis	MN		

US-CL-CURRENT: 514/266.4

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWIC	Draw. De
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☐ 4. Document ID: US 6469013 B2

L5: Entry 4 of 18

File: USPT

Oct 22, 2002

US-PAT-NO: 6469013

DOCUMENT-IDENTIFIER: US 6469013 B2

**\*\* See image for Certificate of Correction \*\***

TITLE: Therapeutic compounds

DATE-ISSUED: October 22, 2002

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Sudbeck; Elise A.	St. Paul	MN		
Cetkovic; Marina	Maplewood	MN		
Malaviya; Ravi	Shoreview	MN		
Liu; Xing-Ping	Minneapolis	MN		

US-CL-CURRENT: 514/266.3; 514/266.4

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWIC	Draw. De
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☐ 5. Document ID: US 6452005 B1

L5: Entry 5 of 18

File: USPT

Sep 17, 2002

US-PAT-NO: 6452005

DOCUMENT-IDENTIFIER: US 6452005 B1

**\*\* See image for Certificate of Correction \*\***

TITLE: JAK-3 inhibitors for treating allergic disorders

DATE-ISSUED: September 17, 2002

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Malaviya; Ravi	Shoreview	MN		
Sudbeck; Elise A.	St. Paul	MN		

US-CL-CURRENT: 544/293

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWIC	Draw De
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☐ 6. Document ID: US 6410545 B1

L5: Entry 6 of 18

File: USPT

Jun 25, 2002

US-PAT-NO: 6410545

DOCUMENT-IDENTIFIER: US 6410545 B1

**\*\* See image for Certificate of Correction \*\***TITLE: Lipid lowering quinazoline dietary supplement composition

DATE-ISSUED: June 25, 2002

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Trieu; Vuong N.	Roseville	MN		
Liu; Xing-Ping	Minneapolis	MN		

US-CL-CURRENT: 514/266.1; 514/266.3

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWIC	Draw De
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☐ 7. Document ID: US 6358962 B2

L5: Entry 7 of 18

File: USPT

Mar 19, 2002

US-PAT-NO: 6358962

h e b b g e e f e ef b e

DOCUMENT-IDENTIFIER: US 6358962 B2

TITLE: 6,7-Dimethoxyquinazolines and therapeutic use thereof

DATE-ISSUED: March 19, 2002

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Liu; Xing-Ping	Minneapolis	MN		
Narla; Rama Krishna	St. Paul	MN		

US-CL-CURRENT: 514/266.4; 544/283, 544/293

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KMC	Draw D
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☐ 8. Document ID: US 6355645 B2

L5: Entry 8 of 18

File: USPT

Mar 12, 2002

US-PAT-NO: 6355645

DOCUMENT-IDENTIFIER: US 6355645 B2

TITLE: Lipid-lowering quinazoline derivative

DATE-ISSUED: March 12, 2002

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Trieu; Vuong N.	Roseville	MN		
Liu; Xing-Ping	Minneapolis	MN		

US-CL-CURRENT: 514/266.1; 514/266.3, 514/266.4, 544/283, 544/286

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KMC	Draw D
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☐ 9. Document ID: US 6326373 B1

L5: Entry 9 of 18

File: USPT

Dec 4, 2001

US-PAT-NO: 6326373

DOCUMENT-IDENTIFIER: US 6326373 B1

**\*\* See image for Certificate of Correction \*\***

TITLE: JAK-3 inhibitors for treating allergic disorders

DATE-ISSUED: December 4, 2001

## INVENTOR-INFORMATION:

h e b b g e e e f e ef b e



NAME	CITY	STATE	ZIP CODE	COUNTRY
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Sudbeck; Elise A.	St. Paul	MN		

US-CL-CURRENT: 514/266.1; 514/266.3, 514/266.4

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	RWC	Draw De
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☐ 10. Document ID: US 6316454 B1

L5: Entry 10 of 18

File: USPT

Nov 13, 2001

US-PAT-NO: 6316454

DOCUMENT-IDENTIFIER: US 6316454 B1

TITLE: 6,7-Dimethoxy-4-anilinoquinazolines

DATE-ISSUED: November 13, 2001

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
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Liu; Xing-Ping	Minneapolis	MN		

US-CL-CURRENT: 514/266.3; 514/266.4, 544/293

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	RWC	Draw De
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L5: Entry 1 of 18

File: USPT

Oct 28, 2003

DOCUMENT-IDENTIFIER: US 6638939 B2

TITLE: 6,7-dimethoxyquinazolines and therapeutic use thereof

Abstract Text (1):

Quinazoline compounds and methods for the treatment of cancer and for the treatment of allergic reactions.

Brief Summary Text (2):

This application relates to quinazoline compounds, compositions and therapeutic methods for the treatment of cancers and treatment of allergic disorders by administering quinazoline compounds.

Brief Summary Text (4):

Quinazoline compounds have been suggested as useful compounds in the treatment of cell growth and differentiation characterized by activity of the human epidermal growth factor receptor type2 (HER2). See, for example, Myers et al., U.S. Pat. No. 5,721,237. Some quinazoline derivatives have been suggested as useful as anti-cancer agents for the treatment of specific receptor tyrosine kinase-expressing cancers, especially those expressing epithelial growth factor (EGF) receptor tyrosine kinase. See, for example, Barker et. al., U.S. Pat. No. 5,457,105. It is generally taught that quinazolines exert their anti-tumor effects via tyrosine kinase inhibition. However, while some quinazoline compounds inhibit the growth of brain tumor cells, others with equally potent tyrosine kinase inhibitory activity fail to do so (Naria et.al., 1998, Clin. Cancer Res. 4:1405-1414; Naria et al., 1998, Clin. Cancer Res. 4:2463-2471).

Brief Summary Text (5):

Several tumors expressing EGF receptors are not killed by quinazoline compounds, whereas some tumors not expressing EGF receptors are. Thus, the cytotoxic activity of quinazoline compounds cannot be attributed to the compound's tyrosine kinase inhibitory activity, and particularly not to the compound's ability to inhibit EGF receptor tyrosine kinase. A chemical structure-activity relationship determining the anti cancer activity of quinazoline derivatives has not been established.

Brief Summary Text (6):

Novel quinazoline compounds may provide potent new therapeutic molecules for the treatment of disorders such as cancers. Methods of using both known and novel quinazoline compounds that employ an understanding of structure-function relationships are needed.

Brief Summary Text (8):

A series of quinazoline compounds were synthesized and analyzed for therapeutic activities, including anti-cancer activities, particularly against EGR receptor-negative leukemias. Specific quinazoline compounds of the invention were found to possess potent and specific tyrosine kinase inhibitory activities affecting cell proliferation and survival. Quinazoline compounds of the invention are demonstrated as useful for the treatment of specific tumors, including breast tumors, brain tumors, and leukemias, particularly EGF receptor-negative leukemias, and to be particularly useful in the treatment of multi-drug resistant leukemias.

Brief Summary Text (9):

The invention provides novel quinazoline compounds of formula I, as disclosed below, as well as therapeutic methods utilizing these compounds.

Drawing Description Text (2):

FIGS. 1A-1C are graphs showing cytotoxic activity of fluoro-substituted dimethoxy quinazoline compounds (F-dmQ) against leukemic NALM-6 cells.

Drawing Description Text (8):

FIGS. 7A and 7B are bar graphs showing the anti-invasive activity of fluoro-substituted quinazoline compounds (F-dmQ) against glioblastoma U373 and breast cancer MDA-MB-231 cells.

Drawing Description Text (11):

FIGS. 10A-10C are graphs showing the inhibition of cancer cell growth in vivo by the quinazolines of the invention.

Detailed Description Text (3):

The terms "quinazoline", "quinazoline compound", and "quinazoline derivative" are used interchangeably in this application to mean compounds of formula I. All scientific and technical terms used in this application have meanings commonly used in the art unless otherwise specified. As used in this application, the following words or phrases have the meanings specified.

Detailed Description Text (6):

The term "conjugate" means a compound formed as a composite between two or more molecules. More specifically, in the present invention, the quinazoline derivative is bonded, for example, covalently bonded, to cell-specific targeting moieties forming a conjugate compound for efficient and specific delivery of the agent to a cell of interest.

Detailed Description Text (10):

Compounds of the invention include quinazolines having the formula: ##STR1##

Detailed Description Text (16):

Additional preferred quinazoline compounds useful in the treatment of tumors are described more fully below and particularly in the Examples. These include: 4-(3',5'-dibromo-4'-methylphenyl)amino-6,7-dimethoxyquinazoline; 4-(2',4',6'-tribromophenyl)amino-6,7-dimethoxyquinazoline; 4-(2',3',5',6'-tetrafluoro-5'-bromophenyl)amino-6,7-dimethoxyquinazoline; 4-(4'-fluorophenyl)amino-6,7-dimethoxyquinazoline; 4-(4'-trifluoromethylphenyl)amino-6,7-dimethoxyquinazoline; and 4-(3',5'-bis-trifluoromethylphenyl)amino-6,7-dimethoxyquinazoline.

Detailed Description Text (24):

The quinazoline compounds of the invention can be formulated as pharmaceutical compositions and administered to a mammalian host, such as a human patient in a variety of forms adapted to the chosen route of administration, i.e., orally or parenterally, by intravenous, intramuscular, topical or subcutaneous routes.

Detailed Description Text (25):

Thus, quinazoline compounds of the invention may be systemically administered, e.g., orally, in combination with a pharmaceutically acceptable vehicle such as an inert diluent or an assimilable edible carrier, or by inhalation or insufflation. They may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets, or may be incorporated directly with the food of the patient's diet. For oral therapeutic administration, the quinazoline compounds may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. The quinazoline compounds may be combined with a fine inert powdered carrier and inhaled by the subject or insufflated. Such compositions and preparations should

contain at least 0.1% quinazoline compounds. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 60% of the weight of a given unit dosage form. The amount of quinazoline compounds in such therapeutically useful compositions is such that an effective dosage level will be obtained.

Detailed Description Text (26):

The tablets, troches, pills, capsules, and the like may also contain the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the quinazoline compounds may be incorporated into sustained-release preparations and devices.

Detailed Description Text (27):

The quinazoline compounds may also be administered intravenously or intraperitoneally by infusion or injection. Solutions of the quinazoline compounds can be prepared in water, optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

Detailed Description Text (28):

The pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions or dispersions or sterile powders comprising the quinazoline compounds which are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. In all cases, the ultimate dosage form must be sterile, fluid and stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions or by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, buffers or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Detailed Description Text (29):

Sterile injectable solutions are prepared by incorporating the quinazoline compounds in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze drying techniques, which yield a powder of the active ingredient plus any additional

desired ingredient present in the previously sterile-filtered solutions.

Detailed Description Text (30):

For topical administration, the quinazoline compounds may be applied in pure form, i.e., when they are liquids. However, it will generally be desirable to administer them to the skin as compositions or formulations, in combination with a dermatologically acceptable carrier, which may be a solid or a liquid.

Detailed Description Text (31):

Useful solid carriers include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina and the like. Other solid carriers include nontoxic polymeric nanoparticles or microparticles. Useful liquid carriers include water, alcohols or glycols or wateralcohol/glycol blends, in which the quinazoline compounds can be dissolved or dispersed at effective levels, optionally with the aid of non-toxic surfactants. Adjuvants such as fragrances and additional antimicrobial agents can be added to optimize the properties for a given use. The resultant liquid compositions can be applied from absorbent pads, used to impregnate bandages and other dressings, or sprayed onto the affected area using pump-type or aerosol sprayers.

Detailed Description Text (33):

Examples of useful dermatological compositions which can be used to deliver the quinazoline compounds to the skin are known to the art; for example, see Jacquet et al. (U.S. Pat. No. 4,608,392), Geria (U.S. Pat. No. 4,992,478), Smith et al. (U.S. Pat. No. 4,559,157) and Wortzman (U.S. Pat. No. 4,820,508).

Detailed Description Text (35):

Generally, the concentration of the quinazoline compounds in a liquid composition, such as a lotion, will be from about 0.1-25 wt-%, preferably from about 0.5-10 wt-%. The concentration in a semi-solid or solid composition such as a gel or a powder will be about 0.1-5 wt-%, preferably about 0.5-2.5 wt-%.

Detailed Description Text (36):

The amount of the quinazoline compounds required for use in treatment will vary not only with the particular salt selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or clinician.

Detailed Description Text (38):

The quinazoline compounds are conveniently administered in unit dosage form; for example, containing 5 to 1000 mg, conveniently 10 to 750 mg, most conveniently, 50 to 500 mg of active ingredient per unit dosage form.

Detailed Description Text (39):

Ideally, the quinazoline compounds should be administered to achieve peak plasma concentrations of from about 0.5 to about 75  $\mu\text{M}$ , preferably, about 1 to 50  $\mu\text{M}$ , most preferably, about 2 to about 30  $\mu\text{M}$ . This may be achieved, for example, by the intravenous injection of a 0.05 to 5% solution of the quinazoline compounds, optionally in saline, or orally administered as a bolus containing about 1-100 mg of the quinazoline compounds. Desirable blood levels may be maintained by continuous infusion to provide about 0.01-5.0 mg/kg/hr or by intermittent infusions containing about 0.4-15 mg/kg of the quinazoline compounds.

Detailed Description Text (40):

The quinazoline compounds may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations; such as multiple inhalations from an insufflator or by application of a plurality of drops into the eye.

Detailed Description Text (41):  
Targeting Quinazolines to Cells

Detailed Description Text (42):  
In a preferred embodiment, the quinazoline compound is targeted to cells where treatment is desired, for example, to leukemia cells, to breast cells, or to other tumor cells. The compound is targeted to the desired cell by conjugation to a targeting moiety that specifically binds the desired cell, thereby directing administration of a conjugated molecule. Useful targeting moieties are ligands which specifically bind cell antigens or cell surface ligands, for example, antibodies against the B cell antigen, CD19 (such as B43) and the like.

Detailed Description Text (43):  
To form the conjugates of the invention, targeting moieties are covalently bonded to sites on the quinazoline compound. The targeting moiety, which is often a polypeptide molecule, is bound to compounds of the invention at reactive sites, including NH.sub.2, SH, CHO, COOH, and the like. Specific linking agents are used to join the compounds. Preferred linking agents are chosen according to the reactive site to which the targeting moiety is to be attached.

Detailed Description Text (45):  
Administration of Quinazolines

Detailed Description Text (46):  
According to the invention, quinazoline compounds may be administered prophylactically, i.e., prior to onset the pathological condition, or the quinazoline compounds may be administered after onset of the reaction, or at both times.

Detailed Description Text (50):  
Synthesis of Quinazoline Derivatives

Detailed Description Text (52):  
The key starting material, 4-chloro-6,7-dimethoxyquinazoline, was prepared according to published procedures (Nomoto, et al., 1990, Chem. Pharm. Bull., 38:1591-1595; Thomas, C. L., 1970, IN:Catalytic Processes and Proven Catalysts, Academic Press, New York, N.Y.) as outlined below in Scheme 1. Specifically, 4,5-dimethoxy-2-nitrobenzoic acid (compound 1) was treated with thionyl chloride to form acid chloride, followed by reacting with ammonia to yield 4,5-dimethoxy-2-nitrobenzamide (compound 2). Compound 2 was reduced with sodium borohydride in the presence of catalytic amounts of copper sulphate to give 4,5-dimethoxy-2-aminobenzamide (compound 3), which was directly refluxed with formic acid to yield 6,7-dimethoxyquinazoline-4(3H)-one (compound 4). Compound 4 was refluxed with phosphorus oxytrichloride to give 4-chloro-6,7-dimethoxyquinazoline (compound 5) in good yield. ##STR4##

Detailed Description Text (53):  
Substituted quinazoline derivatives were prepared by the condensation of 4-chloro-6,7-dimethoxyquinazoline with substituted anilines as outlined below in Scheme 2: ##STR5##

Detailed Description Text (55):  
As discussed above, the novel hydroxy-substituted quinazoline derivatives of the invention were created by reacting the appropriate substituted anilines with the key starting material, 4-chloro-6,7-dimethoxyquinazoline.

Detailed Description Text (59):  
Bromine Substituted Quinazoline Compounds

Detailed Description Text (60):

Bromine substituted quinazoline derivatives were synthesized and characterized as discussed above in Example 1. The structures and physical data are shown below:

Detailed Description Text (65):

4-(3',5'-Dibromo-4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline (H-P97)

Detailed Description Text (75):

4-(3'-Bromo-4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline (H-P154)

Detailed Description Text (104):

Chlorine Substituted Quinazoline Compounds

Detailed Description Text (105):

Chlorine substituted quinazoline derivatives were synthesized and characterized as discussed above in Example 1. The structures and physical data are shown below:

Detailed Description Text (118):

4-(4'-Hydroxyl-2'-chlorophenyl)-amino-6,7-dimethoxy-quinazoline (H-P278)

Detailed Description Text (123):

Iodine Substituted Quinazoline Compounds

Detailed Description Text (124):

Iodine substituted quinazoline derivatives were synthesized as discussed above in Example 1, and analyzed. The structures and physical data are shown below:

Detailed Description Text (129):

4-(4'-Hydroxy3,5-diiodophenyl)-amino-6,7-dimethoxy-quinazoline (H-P294)

Detailed Description Text (136):

OH Group Substituted quinazoline Compounds

Detailed Description Text (137):

OH group substituted quinazoline derivatives were synthesized and characterized as discussed above for Example 1. The structures and physical data are shown below:

Detailed Description Text (138):

4-(3'-Chloro-6'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline (H-P93)

Detailed Description Text (140):

4-(3',5'-Dibromo-4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline (H-P97)

Detailed Description Text (142):

4-(4'-Hydroxylphenyl)-amino-6,7-dimethoxyquinazoline (H-P131)

Detailed Description Text (144):

4-(2'-Hydroxylphenyl)-amino-6,7-dimethoxyquinazoline (H-P132)

Detailed Description Text (150):

4-(3'-Bromo-4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline (H-P154)

Detailed Description Text (193):

Fluorine Substituted Quinazoline Compounds

Detailed Description Text (194):

Fluorine substituted quinazoline derivatives were synthesized and characterized as discussed above for Example 1. The structures and physical data are shown below:

Detailed Description Text (227):

4-(4'-Hydroxyl-3',5'-difluorophenyl)-amino-6,7-dimethoxy-quinazoline (H-P408)

Detailed Description Text (230):

Anti-Tumor Activities of Specific Quinazoline Compounds

Detailed Description Text (231):

The cytotoxicity of the substituted quinazoline derivative compounds against a variety of human tumor cells was evaluated. The relative importance of particular substituent groups on the compounds was also studied. The substituted quinazoline derivative compounds, prepared as described above, were tested, along with DMSO as a control.

Detailed Description Text (233):

The cytotoxicity assay of various compounds against human tumor cell lines was performed using the MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide) assay (Boehringer Mannheim Corp., Indianapolis, Ind.). Briefly, exponentially growing tumor cells were seeded into a 96-well plate at a density of 2.5.times.10.sup.4 cells/well and incubated for 36 hours at 37.degree. C. prior to drug exposure. On the day of treatment, culture medium was carefully aspirated from the wells and replaced with fresh medium containing the quinazoline compounds at concentrations ranging from 0.1 to 250 .mu.M. Triplicate wells were used for each treatment.

Detailed Description Text (254):

Antitumor Activity of Quinazolines In vivo

Detailed Description Text (255):

To test the anti-tumor activity of quinazolines in vivo, cancer cells were implanted and grown in mice in the presence of quinazoline.

Detailed Description Text (258):

The data are shown in FIG. 10A, and demonstrate that treatment of animals with the quinazolines of the invention(HI-P353 and HI-P364) inhibited the growth of breast cancer cell tumors as compared with untreated controls.

Detailed Description Text (261):

The data are shown in FIG. 10B and demonstrate that treatment of animals with the quinazolines of the invention(HI-P353 and HI-P364) inhibited the growth of brain tumors as compared with untreated controls.

Detailed Description Text (263):

The anti-tumor activity of the quinazolines of the invention was also studied with intracranial tumors. Nude mice were first anesthetized with Avertin. Under aseptic conditions in a laminar flow hood, a small hole was drilled at 2 mm to the right of the midline and 2 mm posterior to the bregma. An amount of 4.times.10.sup.5 U87 glioblastoma cells in 10 .mu.L of PBS were intracranially implanted using a Hamilton syringe into the right cerebral hemisphere of mice and a stereotaxic apparatus according to the method described in Huang, H. J. S. et al., J Biol. Chem. 272:2927-2935, 1997.

Detailed Description Text (265):

FIG. 10C shows the survival rate of mice inflicted with intracranial tumors. Treatment of mice with quinazolines(HI-P353 and HI-P364) resulted in prolonged survival as compared with mice treated with vehicle alone.

Detailed Description Paragraph Table (1):

Bromine Substituted Quinazoline Compounds No Name Structure Formula MW 1 P-79  
 ##STR6## C.sub.16 H.sub.14 BrN.sub.3 O.sub.2 360 2 P-88 ##STR7## C.sub.17 H.sub.14  
 BrN.sub.3 O.sub.4 404 3 P-97 ##STR8## C.sub.16 H.sub.13 Br.sub.2 N.sub.3 O.sub.3  
 455 4 P-111 ##STR9## C.sub.17 H.sub.16 BrN.sub.3 O.sub.2 374 5 P-112 ##STR10##



C.sub.16 H.sub.13 Br.sub.2 N.sub.3 O.sub.2 439 6 P-154 ##STR11## C.sub.16 H.sub.14 BrN.sub.3 O.sub.3 376 7 P-160 ##STR12## C.sub.23 H.sub.18 BrN.sub.3 O.sub.2 448 8 P-164 ##STR13## C.sub.17 H.sub.13 BrN.sub.2 O.sub.3 373 9 P-190 ##STR14## C.sub.17 H.sub.16 BrN.sub.3 O.sub.3 389 10 P-210 ##STR15## C.sub.17 H.sub.15 Br.sub.2 N.sub.3 O.sub.2 453 11 P-211 ##STR16## C.sub.17 H.sub.15 Br.sub.2 N.sub.3 O.sub.2 453 12 P-212 ##STR17## C.sub.17 H.sub.15 Br.sub.2 N.sub.3 O.sub.2 453 13 P-214 ##STR18## C.sub.16 H.sub.13 BrFN.sub.3 O.sub.2 378 14 P-222 ##STR19## C.sub.16 H.sub.12 Br.sub.3 N.sub.3 O.sub.2 518 15 P-234 ##STR20## C.sub.17 H.sub.17 N.sub.3 O.sub.2 295 16 P-241 ##STR21## C.sub.17 H.sub.15 Br.sub.2 N.sub.3 O.sub.2 453 17 P-258 ##STR22## C.sub.16 H.sub.15 N.sub.3 O.sub.2 281 18 P-260 ##STR23## C.sub.16 H.sub.14 BrN.sub.3 O.sub.2 360 19 P-261 ##STR24## C.sub.16 H.sub.14 BrN.sub.3 O.sub.2 360 20 P-262 ##STR25## C.sub.16 H.sub.13 Br.sub.2 N.sub.3 O.sub.2 439 21 P-262 ##STR26## C.sub.16 H.sub.13 Br.sub.2 N.sub.3 O.sub.2 439

Detailed Description Paragraph Table (3):

Iodine Substituted Quinazoline Compounds No Name Structure Formula MW 1 P-270 ##STR35## C.sub.16 H.sub.14 IN.sub.3 O.sub.2 407 2 P-271 ##STR36## C.sub.16 H.sub.14 IN.sub.3 O.sub.2 407 3 P-300 ##STR37## C.sub.16 H.sub.14 IN.sub.3 O.sub.2 407 4 P-294 ##STR38## C.sub.16 H.sub.13 I.sub.2 N.sub.3 O.sub.3 549 5 P-299 ##STR39## C.sub.16 H.sub.14 IN.sub.3 O.sub.3 423

Detailed Description Paragraph Table (7):

TABLE 1 Cytotoxic Activity of Bromo Substituted Quinazoline Compounds against Leukemic (NALM-6 & MOLT-3) and Breast Cancer (BT-20) NALM-6 MOLT-3 BT20 IC50 IC50 IC50 Drug (.mu.M) (.mu.M) (.mu.M) HI-P79 142.1 194.9 201.5 HI-P88 >250 >250 >250 HI-P97 >250 >250 26.1 HI-P111 200.6 >250 >250 HI-P154 12.5 9.1 >250 HI-P160 135.2 240.7 25.5 HI-P164 >250 >250 39.2 HI-P190 >250 >250 HI-P210 >250 >250 HI-P211 >250 >250 >250 HI-P212 52.7 54.5 >250 HI-P214 >250 >250 HI-P222 34.0 48.3 >250 HI-P234 >250 >250 >250 HI-P241 >250 >250 >250 HI-P258 >250 >250 HI-P260 32.4 51.3 82.1 HI-P261 72.6 148.5 218.6 HI-P262 >250 >250 >250

Detailed Description Paragraph Table (8):

TABLE 2 Cytotoxic Activity of Chloro Substituted Quinazoline Compounds against Leukemic (NALM-6 & MOLT-3) and Breast Cancer (BT-20) NALM-6 MOLT-3 BT20 IC50 IC50 IC50 Drug (.mu.M) (.mu.M) (.mu.M) HI-P87 95.9 >104.6 >250 HI-P93 >250 >250 >250 HI-P189 >250 >250 >250 HI-P197 39.3 68.0 136.9 HI-P239 29.6 28.7 25.7 HI-P246 >250 >250 HI-P268 215.2 227.4 121.5 HI-P269 >250 >250 >250 HI-P415 67.9 >250 38.1

Detailed Description Paragraph Table (9):

TABLE 3 Cytotoxic Activity of Iodide Substituted Quinazoline Compounds against Leukemic (NALM-6 & MOLT-3), Breast Cancer (BT-20) and Brain Tumor (U373) cells NALM-6 MOLT-3 BT20 U373 IC50 IC50 IC50 IC50 Drug (.mu.M) (.mu.M) (.mu.M) HI-P270 >250 78.9 >250 >250 HI-P271 6.1 9.6 >250 >250 HI-P294 >250 >250 >250 HI-P299 15.4 60.1 >250 >250 HI-P300 58.0 59.1 72.6 116.2

Detailed Description Paragraph Table (11):

TABLE 5 Cytotoxic activity of fluoro-substituted dimethoxy quinazolines on cancer cells. NALM-6 MOLT-3 U373 BT20 PC3 IC50 IC50 IC50 IC50 IC50 Compound (.mu.M) (.mu.M) (.mu.M) (.mu.M) HI-P144 28.1 .+-. 2.6 24.9 .+-. 3.7 49.5 .+-. 11.3 63.4 .+-. 5.5 >250 HI-P214 >250 >250 >250 >250 HI-P218 37.0 .+-. 5.8 33.2 .+-. 3.3 29.9 .+-. 7.3 37.62 .+-. 5.2 126.1 .+-. 5.8 HI-P219 22.3 .+-. 3.0 41.3 .+-. 4.4 83.6 .+-. 6.5 44.2 .+-. 10.9 58.3 .+-. 3.2 HI-P221 100.5 .+-. 4.8 98.73 .+-. 3.8 28.8 .+-. 12.7 30.67 .+-. 7.9 >250 HI-P223 39.5 .+-. 8.0 40.8 .+-. 15.1 32.1 .+-. 3.9 27.56 .+-. 8.6 >250 HI-P224 20.15 .+-. 8.1 23.3 .+-. 7.7 22.4 .+-. 5.9 58.33 .+-. 5.8 >250 HI-P228 57.3 .+-. 24.8 237.1 .+-. 4.8 >250 >250 >250 HI-P232 41.4 .+-. 6.9 43.6 .+-. 2.3 207.7 .+-. 18.1 70.54 .+-. 8.2 88.9 .+-. 17.2 HI-P264 47.0 .+-. 19.5 70.9 .+-. 17.3 53.3 .+-. 6.7 33.33 .+-. 7.5 >250 HI-P352 7.1 .+-. 1.8 21.8 .+-. 1.7 65.5 .+-. 11.2 50.3 .+-. 14.8 72.6 .+-. 2.5 HI-P353 6.1 .+-. 1.4 17.4 .+-. 1.5 14.5 .+-. 7.6 14.1 .+-. 3.3 64.9 .+-. 11.9 HI-P364 7.9 .+-. 1.9 25.3 .+-. 9.1 27.7 .+-. 1.2 40.1 .+-. 8.6 >250 HI-P365 86.5 .+-. 3.4 110.7 .+-. 7.5

>250 >250 >250 HI-P366 52.8 .+-. 14.0 137.2 .+-. 10.3 55.5 .+-. 13.2 61.7 .+-. 12.1  
>250 HI-P369 >250 >250 >250 >250 >250 HI-P408 116.3 .+-. 17.8 228.5 .+-. 20.8 >250  
>250 >250

Other Reference Publication (2):

Nomoto, Y. et al., "Studies on Cardiotonic Agents. I. Synthesis of Some Quinazoline Derivatives," Chem. Pharm. Bull., vol. 38, No. 6, pp. 1591-1595 (1990).

Other Reference Publication (8):

Budesinsky, Z. et al., "A New Synthesis of the Quinazoline Nucleus", Collection of Czechoslovak Chemical Communications, vol. 37, No. 8, pp. 2779-2785 (Aug. 1972).

Other Reference Publication (12):

Higashino, T. et al., "Reactions of the anion of quinazoline Reissert compound (3-benzoyl-3,4-dihydro-4-quinazollinecarbon itrile) with electrophiles", Chemical & Pharmaceutical Bulletin, vol. 33, No. 3, pp. 950-961 (Mar. 1985).

Other Reference Publication (18):

Miyashita, A. et al., "An Approach to the Synthesis of a Papaverine Analogue Containing a Quinazoline Ring System," Heterocycles, vol. 40, No. 2, pp. 653-660 (1995).

Other Reference Publication (20):

Myers, M. R. et al., "The Preparation and SAR of 4-(Anilino), 4-(Phenoxy), and 4-(Thiopenoxy)-Quinazolines: Inhibitors of p56.sup.lck and EGF-R Tyrosine Kinase Activity," Bioorganic & Medicinal Chemistry Letters, vol. 7, No. 4, pp. 417-420 (1997).

Other Reference Publication (21):

Narla, R. K. et al., "4-(3'-Bromo-4' hydroxyphenyl)-amino-6,7-dimethoxyquinazoline: A Novel Quinazoline Derivative with Potent Cytotoxic Activity against Human Glioblastoma Cells," Clinical Cancer Research, vol. 4, pp. 1405-1414 (Jun. 1998).

In summary, the studies detailed herein provide experimental evidence that JAK3, a member of Janus family protein tyrosine kinases, plays a pivotal role in IgE receptor-mediated mast cell responses. Furthermore, the data demonstrate that targeting JAK3 in mast cells with WHI-P131 [4-(4'-hydroxylphenyl)amino-6,7-dimethoxyquinazoline], a potent and specific inhibitor of JAK3, abrogates mast cell degranulation and release of allergic mediators in vitro and, at nontoxic dose levels, prevents IgE receptor/Fc.εRI mediated anaphylactic reactions, including fatal anaphylactic shock, in vivo.

Detailed Description Paragraph Table (1):

TABLE 2 Second generation quinazoline designs targeting JAK3 kinase active site. All compounds were predicted to interact favorably with JAK3 kinase residues. NA = not applicable. ##STR2## ##STR3## ##STR4## ##STR5## Molecular Compound Surface Volume Name R3' R4' R5' R6' R7' Area (.ANG..<sup>sup.2</sup>) (.ANG..<sup>sup.3</sup>) Q1 H OH OH H NA 275 273 Q2 Br H OH CH.sub.2 OH NA 300 288 Q3 Br H OH NH.sub.2 NA 283 274 Q4 Br H OH NO.sub.2 NA 300 294 Q5 H OH Br OH NA 322 308 Q6 H OH Br CH.sub.2 OH NA 327 323 Q7 H OH Br NH.sub.2 NA 318 311 Q8 H OH Br NO.sub.2 NA 340 329 Q9 H OH Br H NA 317 295 Q10 H OH OH H NA 308 306 Q11 H OH CH.sub.2 OH H NA 314 321 Q12 H OH NH.sub.2 H NA 309 309 Q13 H OH NO.sub.2 H NA 329 331 Q14 H OH Br H OH 336 317 Q15 H OH Br H CH.sub.2 OH 349 334 Q16 H OH Br H NH.sub.2 336 321 Q17 H OH Br H NO.sub.2 359 340

Detailed Description Paragraph Table (2):

TABLE 1 Predicted interaction of quinazolines with JAK3 kinase active site and measured inhibition values (IC<sub>sub.50</sub> values) for JAK3 kinase. ##STR10## Pre-Molec- dicted ular Com- binding Surface Molecular pound to Area Volume IC<sub>sub.50</sub> Name R.sub.1 R.sub.2 R.sub.3 R.sub.4 JAK3 (.ANG..<sup>sup.2</sup>) (.ANG..<sup>sup.3</sup>) (.μM) WHI- H OH H H favor- 726 261 78 P131 able WHI- H OH Br H favor- 296 284 128 P154 able WHI- H H OH H favor- 273 260 3 P180 able WHI- Br OH Br H favor- 314 307 11 P97 able WHI- H H Br H less 278 272 >300 P79 favor- able WHI- H CH.sub.3 Br H less 309 291 >300 P111 favor- able WHI- Br H H Br less 306 297 >200 P112 favor- able WHI- H H H OH less 269 262 >300 P132 favor- 264 able WHI- H H H H less 266 252 >300 P258 favor- able

Other Reference Publication (52):

Narla, R. et al., "4-(3'-Bromo-4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline: A Novel Quinazoline Derivative with Potent Cytotoxic Activity against Human Glioblastoma Cells", Clin. Cancer Res., vol. 4, No. 6, pp. 1405-1414 (Jun. 1998).

Other Reference Publication (54):

Nomoto, Y. et al., "Studies on Cardiotonic Agents. I. Synthesis of Some Quinazoline Derivatives", Chem. Pharm. Bull., vol. 38, No. 6, pp. 1591-1595 (Jun. 1990).

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☐ 1. Document ID: US 6638939 B2

L5: Entry 1 of 18

File: USPT

Oct 28, 2003

US-PAT-NO: 6638939

DOCUMENT-IDENTIFIER: US 6638939 B2

TITLE: 6,7-dimethoxyquinazolines and therapeutic use thereof

DATE-ISSUED: October 28, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Liu; Xing-Ping	Minneapolis	MN		
Narla; Rama Krishna	St. Paul	MN		

US-CL-CURRENT: 514/266.4; 544/293

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequence	Attachment	Claims	KWIC	Draw D
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☐ 2. Document ID: US 6552027 B2

L5: Entry 2 of 18

File: USPT

Apr 22, 2003

US-PAT-NO: 6552027

DOCUMENT-IDENTIFIER: US 6552027 B2

TITLE: Quinazolines for treating brain tumor

DATE-ISSUED: April 22, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Narla; Rama Krishna	St. Paul	MN		
Liu; Xing-Ping	Minneapolis	MN		

US-CL-CURRENT: 514/266.4

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWIC	Draw De
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☐ 3. Document ID: US 6495556 B2

L5: Entry 3 of 18

File: USPT

Dec 17, 2002

US-PAT-NO: 6495556

DOCUMENT-IDENTIFIER: US 6495556 B2

**\*\* See image for Certificate of Correction \*\***TITLE: Dimethoxy quinazolines for treating diabetes

DATE-ISSUED: December 17, 2002

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Sudbeck; Elise A.	St. Paul	MN		
Cetkovic; Marina	Maplewood	MN		
Malaviya; Ravi	Shoreview	MN		
Liu; Xing-Ping	Minneapolis	MN		

US-CL-CURRENT: 514/266.4

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWIC	Draw De
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☐ 4. Document ID: US 6469013 B2

L5: Entry 4 of 18

File: USPT

Oct 22, 2002

US-PAT-NO: 6469013

DOCUMENT-IDENTIFIER: US 6469013 B2

**\*\* See image for Certificate of Correction \*\***

TITLE: Therapeutic compounds

DATE-ISSUED: October 22, 2002

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Sudbeck; Elise A.	St. Paul	MN		
Cetkovic; Marina	Maplewood	MN		
Malaviya; Ravi	Shoreview	MN		
Liu; Xing-Ping	Minneapolis	MN		

US-CL-CURRENT: 514/266.3; 514/266.4

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWIC	Draw De
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☐ 5. Document ID: US 6452005 B1

L5: Entry 5 of 18

File: USPT

Sep 17, 2002

US-PAT-NO: 6452005

DOCUMENT-IDENTIFIER: US 6452005 B1

**\*\* See image for Certificate of Correction \*\***

TITLE: JAK-3 inhibitors for treating allergic disorders

DATE-ISSUED: September 17, 2002

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Malaviya; Ravi	Shoreview	MN		
Sudbeck; Elise A.	St. Paul	MN		

US-CL-CURRENT: 544/293

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWIC	Draw De
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☐ 6. Document ID: US 6410545 B1

L5: Entry 6 of 18

File: USPT

Jun 25, 2002

US-PAT-NO: 6410545

DOCUMENT-IDENTIFIER: US 6410545 B1

**\*\* See image for Certificate of Correction \*\***TITLE: Lipid lowering quinazoline dietary supplement composition

DATE-ISSUED: June 25, 2002

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Trieu; Vuong N.	Roseville	MN		
Liu; Xing-Ping	Minneapolis	MN		

US-CL-CURRENT: 514/266.1; 514/266.3

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWIC	Draw De
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☐ 7. Document ID: US 6358962 B2

L5: Entry 7 of 18

File: USPT

Mar 19, 2002

US-PAT-NO: 6358962

h e b b g e e e f e f b e

DOCUMENT-IDENTIFIER: US 6358962 B2

TITLE: 6,7-Dimethoxyquinazolines and therapeutic use thereof

DATE-ISSUED: March 19, 2002

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Liu; Xing-Ping	Minneapolis	MN		
Narla; Rama Krishna	St. Paul	MN		

US-CL-CURRENT: 514/266.4; 544/283, 544/293

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWMC	Draw De
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☐ 8. Document ID: US 6355645 B2

L5: Entry 8 of 18

File: USPT

Mar 12, 2002

US-PAT-NO: 6355645

DOCUMENT-IDENTIFIER: US 6355645 B2

TITLE: Lipid-lowering quinazoline derivative

DATE-ISSUED: March 12, 2002

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Trieu; Vuong N.	Roseville	MN		
Liu; Xing-Ping	Minneapolis	MN		

US-CL-CURRENT: 514/266.1; 514/266.3, 514/266.4, 544/283, 544/286

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWMC	Draw De
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☐ 9. Document ID: US 6326373 B1

L5: Entry 9 of 18

File: USPT

Dec 4, 2001

US-PAT-NO: 6326373

DOCUMENT-IDENTIFIER: US 6326373 B1

**\*\* See image for Certificate of Correction \*\***

TITLE: JAK-3 inhibitors for treating allergic disorders

DATE-ISSUED: December 4, 2001

## INVENTOR-INFORMATION:

h e b b g e e f e ef b e

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Malavia; Ravi	Shoreview	MN		
Sudbeck; Elise A.	St. Paul	MN		

US-CL-CURRENT: 514/266.1; 514/266.3, 514/266.4

## Search Results

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWIC	Draw De
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Logout 10. Document ID: US 6316454 B1

L5: Entry 10 of 18

File: USPT

Nov 13, 2001

US-PAT-NO: 6316454

DOCUMENT-IDENTIFIER: US 6316454 B1

TITLE: 6,7-Dimethoxy-4-anilinoquinazolines

DATE-ISSUED: November 13, 2001

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Narla; Rama Krishna	St. Paul	MN		
Liu; Xing-Ping	Minneapolis	MN		

US-CL-CURRENT: 514/266.3; 514/266.4, 544/293

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWIC	Draw De
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Dec 4, 2001

DOCUMENT-IDENTIFIER: US 6326373 B1

**\*\* See image for Certificate of Correction \*\***

TITLE: JAK-3 inhibitors for treating allergic disorders

Brief Summary Text (13):

We have now discovered that IgE/antigen induced degranulation and mediator release are substantially reduced in Jak.sup.-/- mast cells from JAK3-null mice that generated by targeted disruption of Jak3 gene in embryonic stem cells. Furthermore, treatment of mouse, rat, as well as human mast cells with 4-(4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline (WHI-P131), a rationally designed potent and specific inhibitor of JAK3, inhibited degranulation and proinflammatory mediator release after IgE receptor/Fc.epsilon.RI crosslinking. In vivo administration of this potent JAK3 inhibitor prevented mast cell degranulation and development of cutaneous, as well as systemic, fatal anaphylaxis in mice. Thus, JAK3 plays a pivotal role in IgE receptor/Fc.epsilon.RI mediated mast cell responses both in vitro and in vivo.

Drawing Description Text (6):

FIG. 2B is a model of the catalytic site of JAK3 with docked quinazolines WHI-P131 (multicolor), WHI-P132 (pink), and WHI-P154 (yellow). Each compound fits into the binding site, but WHI-P132 (shown to be inactive against JAK3 in biological assays). WHI-P132 lacks an OH group in a location to bind with Asp967. WHI-P131 and WHI-P154, with OH groups at the C4' position of the phenyl ring, are able to form a favorable interaction with Asp967 of JAK3, which may contribute to their enhanced inhibition activity.

Drawing Description Text (7):

FIG. 2C is a diagram showing features of dimethoxy quinazoline derivatives which are predicted to aid binding to JAK3 catalytic site.

Drawing Description Text (30):

FIG. 15 is a diagram showing features of quinazoline derivatives which aid binding to the JAK3 catalytic site.

Detailed Description Text (5):

JAK3-null mice did not develop an anaphylactic reaction to bovine albumin whereas wild-type mice did. Treatment of mouse, rat, as well as human mast cells with 4-(4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline (Compound 1), a potent and specific inhibitor of JAK3, inhibited degranulation and proinflammatory mediator release after IgE receptor/Fc.epsilon.RI crosslinking. Effective mast cell inhibitory plasma concentrations of Compound 1 were achieved in vivo at non-toxic dose levels.

Detailed Description Text (25):

Preferred JAK-3 inhibitors include 4-(4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline (P131), 4-(3'-bromo-4'-hydroxylphenyl)-amino-6,7-diethoxyquinazoline (P154), 4-(3'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline, (P180) and 4-(3',5'-dibromo-4'-hydroxy phenyl)-6,7-dinethoxyquinazoline (P97) or a pharmaceutically acceptable salt thereof.

Detailed Description Text (74):

An analysis of the JAK3 model revealed specific features of the catalytic site which can be described as a quadrilateral-shaped pocket (FIG. 1C). The opening of the pocket is defined by residues Pro906, Ser907, Gly908, Asp912, Arg953, Gly829, Leu828, and Tyr904 (blue residues in FIG. 1C). The far wall deep inside the pocket is lined with Leu905 (backbone portion), Glu903, Met902, Lys905, and Asp967 (pink residues, FIG. 1C). The floor of the pocket is lined by Leu905 (side chain portion), Val884, Leu956, and Ala966 (yellow residues, FIG. 1C). The residues defining the roof of the pocket include Leu828, Gly829, Lys830, and Gly831 (uppermost blue residues, FIG. 1C). FIGS. 1C and 2A illustrate that the catalytic site of the JAK3 model has approximate dimensions of 8 .ANG..<sup>3</sup> by 11 .ANG..<sup>3</sup> by 20 .ANG..<sup>3</sup> and an available volume for binding of approximately 533 .ANG..<sup>3</sup>. According to the model, the solvent exposed opening to the binding region would allow inhibitors to enter and bind if the molecule contains some planarity. Asp 1017 can form a hydrogen bond with a 3' or 4' OH group of a quinazoline bound to the catalytic site, and Leu955 can interact with a quinazoline ring nitrogen hydrophilic substituent at C5' and C6' on the phenyl ring of quinazoline would also enhance binding to JAK3. Steric hinderence with Met 952 prevents the addition of a non-hydrogen substituent at C2. Modifications to increase the volume of the inhibitor in the pocket, for example to a volume of about 200 .ANG..<sup>3</sup> -500 .ANG..<sup>3</sup>, 225-350 .ANG..<sup>3</sup> will provide more potent compounds.

Detailed Description Text (83):

The computer docking procedure was used to predict how well potential inhibitors could fit into and bind to the catalytic site of JAK3 and result in kinase inhibition (FIG. 2B). The dimethoxyquinazoline compound WHI-P258 (4-(phenyl)-amino-6,7-dimethoxyquinazoline) contains two methoxy groups on the quinazoline moiety but no other ring substituents. Molecular modeling studies using the homology model of JAK3 kinase domain suggested that WHI-P258 would fit into the catalytic site of JAK3, but probably would not bind very tightly due to limited hydrogen bonding interactions. Asp967, a key residue in the catalytic site of JAK3, can form a hydrogen bond with molecules binding to the catalytic site, if such molecules contain a hydrogen bond donor group such as an OH group. WHI-P258, however, does not contain an OH group and therefore would not interact as favorably with Asp967. We postulated that the presence of an OH group at the 4' position of the phenyl ring of WHI-P258 would result in stronger binding to JAK3 because of added interactions with Asp967. A series of dimethoxyquinazoline compounds were designed and synthesized to test this hypothesis.

Detailed Description Text (85):

The conformations of the energy-minimized models of the compounds listed in Table 1 were relatively planar, with dihedral angles of approximately 4-18.degree. between the phenyl ring and quinazoline ring system. This conformation allows the compounds to fit more easily into the catalytic site of JAK3. All of the listed compounds contain a ring nitrogen (N1), which can form a hydrogen bond with NH of Leu905 in the hinge region of JAK3. When N1 is protonated, the NH can instead interact with the carbonyl group in Leu905 of JAK3. The presence of an OH group at the 4' position on the phenyl ring was anticipated to be particularly important for binding to the catalytic site of JAK3. WHI-P131 (estimated  $K_{sub.i} = 2.3 \text{ .}\mu\text{M}$ ), WHI-P154 (estimated  $K_{sub.i} = 1.4 \text{ .}\mu\text{M}$ ), WHI-P97 (estimated  $K_{sub.i} = 0.6 \text{ .}\mu\text{M}$ ) shown in Table 1 were predicted to have favorable binding to JAK3 and potent JAK3 inhibitory activity because they contain a 4' OH group on the phenyl ring which can form a hydrogen bond with Asp967 of JAK3, contributing to enhanced binding. By comparison, the 2' OH group of WHI-P132 is not in the right orientation to interact with Asp967 and it probably would form an intramolecular hydrogen bond with the quinazoline ring nitrogen, which may contribute to a significantly lower affinity of WHI-P132 for the catalytic site of JAK3.

Detailed Description Text (91):

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4,5-Dimethoxy-2-nitrobenzoic acid (3) was treated with thionyl chloride and then reacted with ammonia to give 4,5-dimethoxy-2-nitrobenzamide (4) as described by F. Nomoto et al. Chem. Pharm. Bull., 1990, 38, 1591-1595. The nitro group in compound (4) was reduced with sodium borohydride in the presence of copper sulfate (see C. L. Thomas, Catalytic Processes and Proven Catalysts, Academic Press, New York (1970)) to give 4,5-dimethoxy-2-aminobenzamide (5) which was cyclized by refluxing with formic acid to give 6,7-dimethoxyquinazoline-4(3H)-one (6). Compound (6) was refluxed with phosphorus oxytrichloride to provide the common synthetic precursor (7).

Detailed Description Text (96):

4,5-Dimethoxy-2-nitrobenzamide 3: Yield 88.50%; mp 197.0-200.0.degree. C.; <sup>1</sup>H NMR(DMSO-d<sub>6</sub>) δ 7.60 (s, 2H, --NH<sub>2</sub>), 7.57 (s, 1H, 6-H), 7.12 (s, 1H, 3-H), 3.90 (s, 3H, --OCH<sub>3</sub>), 3.87 (s, 3H, --OCH<sub>3</sub>); IR (KBr) 3454, 2840, 1670, 1512, 1274, 1227 cm<sup>-1</sup>; GC/MS m/z 226 (M<sup>+</sup>, 10), 178(99), 163(100), 135(51).

Detailed Description Text (99):

4-(3',5'-Dibromo-4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline WHI-P97: Yield 72.80%; mp>300.0.degree. C.; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 9.71 (s, 1H, --NH), 9.39 (s, 1H, --OH), 8.48 (s, 1H, 2-H), 8.07 (s, 2H, 2', 6'-H), 7.76 (s, 1H, 5-H), 7.17 (s, 1H, 8-H), 3.94 (s, 3H, --OCH<sub>3</sub>), 3.91 (s, 3H, --OCH<sub>3</sub>); IR (KBr) 3504, 3419, 2868, 1627, 1512, 1425, 1250, 1155 cm<sup>-1</sup>; GC/MS m/z 456 (M<sup>+</sup>+1, 54), 455 (M<sup>+</sup>, 100), 454 (M<sup>+</sup>-1, 78), 439 (M<sup>+</sup>--OH, 8), 376 (M<sup>+</sup>+1-Br, 10), 375 (M<sup>+</sup>-Br, 11), 360 (5); Anal. (C<sub>16</sub>H<sub>13</sub>Br<sub>2</sub>N<sub>3</sub>O<sub>3</sub>) C, H, N.

Detailed Description Text (102):

4-(4'-Hydroxylphenyl)-amino-6,7-dimethoxyquinazoline WHI-P131: Yield 84.29%; mp 245.0-248.0.degree. C.; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 11.21 (s, 1H, --NH), 9.70 (s, 1H, --OH), 8.74 (s, 1H, 2-H), 8.22 (s, 1H, 5-H), 7.40 (d, 2H, J=8.9 Hz, 2', 6'-H), 7.29 (s, 1H, 8-H), 6.85 (d, 2H, J=8.9 Hz, 3', 5'-H), 3.98 (s, 3H, --OCH<sub>3</sub>), 3.97 (s, 3H, --OCH<sub>3</sub>); IR (KBr) 3428, 2836, 1635, 1516, 1443, 1234 cm<sup>-1</sup>; GC/MS m/z 298 (M<sup>+</sup>+1, 100), 297 (M<sup>+</sup>, 27), 296 (M<sup>+</sup>-1, 12); Anal. (C<sub>16</sub>H<sub>15</sub>N<sub>3</sub>O<sub>3</sub>·HCl) C, H, N.

Detailed Description Text (103):

4-(2'-Hydroxylphenyl)-amino-6,7-dimethoxyquinazoline WHI-P132: Yield 82.49%; mp 255.0-258.0.degree. C.; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 9.78 (s, 1H, --NH), 9.29 (s, 1H, --OH), 8.33 (s, 1H, 2-H), 7.85 (s, 1H, 5-H), 7.41-6.83 (m, 4H, 3', 4', 5', 6'-H), 7.16 (s, 1H, 8-H), 3.93 (s, 3H, --OCH<sub>3</sub>), 3.92 (s, 3H, --OCH<sub>3</sub>); IR (KBr) 3500, 3425, 2833, 1625, 1512, 1456, 1251, 1068 cm<sup>-1</sup>; GC/MS m/z 298 (M<sup>+</sup>+1, 9), 297 (M<sup>+</sup>, 57), 281 (M<sup>+</sup>+1-OH, 23), 280 (M<sup>+</sup>-OH, 100); Anal. (C<sub>16</sub>H<sub>15</sub>N<sub>3</sub>O<sub>3</sub>·HCl) C, H, N.

Detailed Description Text (104):

4-(3'-Bromo-4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline WHI-P154: Yield 89.90%; mp 233.0-233.5.degree. C.; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 10.08 (s, 1H, --NH), 9.38 (s, 1H, --OH), 8.40 (s, 1H, 2-H), 7.89 (d, 1H, J<sub>2',6'</sub> = 2.7 Hz, 2'-H), 7.75 (s, 1H, 5-H), 7.55 (dd, 1H, J<sub>5',6'</sub> = 9.0 Hz, J<sub>2',6'</sub> = 2.7 Hz, 6'-H), 7.14 (s, 1H, 8-H), 6.97 (d, 1H, J<sub>5',6'</sub> = 9.0 Hz, 5'-H), 3.92 (s, 3H, --OCH<sub>3</sub>), 3.90 (s, 3H, --OCH<sub>3</sub>); IR (KBr) 3431, 2841, 1624, 1498, 1423, 1244 cm<sup>-1</sup>; GC/MS m/z 378 (M<sup>+</sup>+2, 91), 377 (M<sup>+</sup>+1, 37), 376 (M<sup>+</sup>, 100), 360 (M<sup>+</sup>+4, 298 (19), 282 (7); Anal. (C<sub>16</sub>H<sub>14</sub>BrN<sub>3</sub>O<sub>3</sub>·HCl) C, H, N.

Detailed Description Text (141):

Effects of Dimethoxy Quinoxalines on JAK-3 Activity

Detailed Description Text (173):

In summary, the studies detailed herein provide experimental evidence that JAK3, a member of Janus family protein tyrosine kinases, plays a pivotal role in IgE receptor-mediated mast cell responses. Furthermore, the data demonstrate that targeting JAK3 in mast cells with WHI-P131 [4-(4'-hydroxylphenyl)amino-6,7-dimethoxyquinazoline], a potent and specific inhibitor of JAK3, abrogates mast cell degranulation and release of allergic mediators in vitro and, at nontoxic dose levels, prevents IgE receptor/Fc.εRI mediated anaphylactic reactions, including fatal anaphylactic shock, in vivo.

Detailed Description Paragraph Table (1):

TABLE 2 Second generation quinazoline designs targeting JAK3 kinase active site. All compounds were predicted to interact favorably with JAK3 kinase residues. NA = not applicable. ##STR2## ##STR3## ##STR4## ##STR5## Molecular Molecular Compound Surface Volume Name R3' R4' R5' R6' R7' Area (.ANG..<sup>2</sup>) (.ANG..<sup>3</sup>) Q1 H OH OH H NA 275 273 Q2 Br H OH CH.sub.2 OH NA 300 288 Q3 Br H OH NH.sub.2 NA 283 274 Q4 Br H OH NO.sub.2 NA 300 294 Q5 H OH Br OH NA 322 308 Q6 H OH Br CH.sub.2 OH NA 327 323 Q7 H OH Br NH.sub.2 NA 318 311 Q8 H OH Br NO.sub.2 NA 340 329 Q9 H OH Br H NA 317 295 Q10 H OH OH H NA 308 306 Q11 H OH CH.sub.2 OH H NA 314 321 Q12 H OH NH.sub.2 H NA 309 309 Q13 H OH NO.sub.2 H NA 329 331 Q14 H OH Br H OH 336 317 Q15 H OH Br H CH.sub.2 OH 349 334 Q16 H OH Br H NH.sub.2 336 321 Q17 H OH Br H NO.sub.2 359 340

Detailed Description Paragraph Table (2):

TABLE 1 Predicted interaction of quinazolines with JAK3 kinase active site and measured inhibition values (IC<sub>50</sub> values) for JAK3 kinase. ##STR10## Pre-Molec- dicted ular Com- binding Surface Molecular pound to Area Volume IC<sub>50</sub> Name R.sub.1 R.sub.2 R.sub.3 R.sub.4 JAK3 (.ANG..<sup>2</sup>) (.ANG..<sup>3</sup>) (.μM) WHI- H OH H H favor- 726 261 78 P131 able WHI- H OH Br H favor- 296 284 128 P154 able WHI- H H OH H favor- 273 260 3 P180 able WHI- Br OH Br H favor- 314 307 11 P97 able WHI- H H Br H less 278 272 >300 P79 favor- able WHI- H CH.sub.3 Br H less 309 291 >300 P111 favor- able WHI- Br H H Br less 306 297 >200 P112 favor- able WHI- H H H OH less 269 262 >300 P132 favor- 264 able WHI- H H H H less 266 252 >300 P258 favor- able

Other Reference Publication (52):

Narla, R. et al., "4-(3'-Bromo-4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline: A Novel Quinazoline Derivative with Potent Cytotoxic Activity against Human Glioblastoma Cells", Clin. Cancer Res., vol. 4, No. 6, pp. 1405-1414 (Jun. 1998).

Other Reference Publication (54):

Nomoto, Y. et al., "Studies on Cardiotonic Agents. I. Synthesis of Some Quinazoline Derivatives", Chem. Pharm. Bull., vol. 38, No. 6, pp. 1591-1595 (Jun. 1990).

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Dec 4, 2001

DOCUMENT-IDENTIFIER: US 6326373 B1

**\*\* See image for Certificate of Correction \*\***

TITLE: JAK-3 inhibitors for treating allergic disorders

Brief Summary Text (13):

We have now discovered that IgE/antigen induced degranulation and mediator release are substantially reduced in Jak.sup.-/- mast cells from JAK3-null mice that generated by targeted disruption of Jak3 gene in embryonic stem cells. Furthermore, treatment of mouse, rat, as well as human mast cells with 4-(4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline (WHI-P131), a rationally designed potent and specific inhibitor of JAK3, inhibited degranulation and proinflammatory mediator release after IgE receptor/Fc.epsilon.RI crosslinking. In vivo administration of this potent JAK3 inhibitor prevented mast cell degranulation and development of cutaneous, as well as systemic, fatal anaphylaxis in mice. Thus, JAK3 plays a pivotal role in IgE receptor/Fc.epsilon.RI mediated mast cell responses both in vitro and in vivo.

Drawing Description Text (6):

FIG. 2B is a model of the catalytic site of JAK3 with docked quinazolines WHI-P131 (multicolor), WHI-P132 (pink), and WHI-P154 (yellow). Each compound fits into the binding site, but WHI-P132 (shown to be inactive against JAK3 in biological assays). WHI-P132 lacks an OH group in a location to bind with Asp967. WHI-P131 and WHI-P154, with OH groups at the C4' position of the phenyl ring, are able to form a favorable interaction with Asp967 of JAK3, which may contribute to their enhanced inhibition activity.

Drawing Description Text (7):

FIG. 2C is a diagram showing features of dimethoxy quinazoline derivatives which are predicted to aid binding to JAK3 catalytic site.

Drawing Description Text (30):

FIG. 15 is a diagram showing features of quinazoline derivatives which aid binding to the JAK3 catalytic site.

Detailed Description Text (5):

JAK3-null mice did not develop an anaphylactic reaction to bovine albumin whereas wild-type mice did. Treatment of mouse, rat, as well as human mast cells with 4-(4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline (Compound 1), a potent and specific inhibitor of JAK3, inhibited degranulation and proinflammatory mediator release after IgE receptor/Fc.epsilon.RI crosslinking. Effective mast cell inhibitory plasma concentrations of Compound 1 were achieved in vivo at non-toxic dose levels.

Detailed Description Text (25):

Preferred JAK-3 inhibitors include 4-(4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline (P131), 4-(3'-bromo-4'-hydroxylphenyl)-amino-6,7-diethoxyquinazoline (P154), 4-(3'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline, (P180) and 4-(3',5'-dibromo-4'-hydroxy phenyl)-6,7-dinethoxyquinazoline (P97) or a pharmaceutically acceptable salt thereof.

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Detailed Description Text (74):

An analysis of the JAK3 model revealed specific features of the catalytic site which can be described as a quadrilateral-shaped pocket (FIG. 1C). The opening of the pocket is defined by residues Pro906, Ser907, Gly908, Asp912, Arg953, Gly829, Leu828, and Tyr904 (blue residues in FIG. 1C). The far wall deep inside the pocket is lined with Leu905 (backbone portion), Glu903, Met902, Lys905, and Asp967 (pink residues, FIG. 1C). The floor of the pocket is lined by Leu905 (side chain portion), Val884, Leu956, and Ala966 (yellow residues, FIG. 1C). The residues defining the roof of the pocket include Leu828, Gly829, Lys830, and Gly831 (uppermost blue residues, FIG. 1C). FIGS. 1C and 2A illustrate that the catalytic site of the JAK3 model has approximate dimensions of 8 .ANG..<sup>times.11</sup> .ANG..<sup>times.20</sup> .ANG. and an available volume for binding of approximately 533 .ANG..<sup>sup.3</sup>. According to the model, the solvent exposed opening to the binding region would allow inhibitors to enter and bind if the molecule contains some planarity. Asp 1017 can form a hydrogen bond with a 3' or 4' OH group of a quinazoline bound to the catalytic site, and Leu955 can interact with a quinazoline ring nitrogen hydrophilic substituent at C5' and C6' on the phenyl ring of quinazoline would also enhance binding to JAK3. Steric hinderence with Met 952 prevents the addition of a non-hydrogen substituent at C2. Modifications to increase the volume of the inhibitor in the pocket, for example to a volume of about 200 .ANG..<sup>sup.3</sup> -500 .ANG..<sup>sup.3</sup>, 225-350 .ANG..<sup>sup.3</sup> will provide more potent compounds.

Detailed Description Text (83):

The computer docking procedure was used to predict how well potential inhibitors could fit into and bind to the catalytic site of JAK3 and result in kinase inhibition (FIG. 2B). The dimethoxyquinazoline compound WHI-P258 (4-(phenyl)-amino-6,7-dimethoxyquinazoline) contains two methoxy groups on the quinazoline moiety but no other ring substituents. Molecular modeling studies using the homology model of JAK3 kinase domain suggested that WHI-P258 would fit into the catalytic site of JAK3, but probably would not bind very tightly due to limited hydrogen bonding interactions. Asp967, a key residue in the catalytic site of JAK3, can form a hydrogen bond with molecules binding to the catalytic site, if such molecules contain a hydrogen bond donor group such as an OH group. WHI-P258, however, does not contain an OH group and therefore would not interact as favorably with Asp967. We postulated that the presence of an OH group at the 4' position of the phenyl ring of WHI-P258 would result in stronger binding to JAK3 because of added interactions with Asp967. A series of dimethoxyquinazoline compounds were designed and synthesized to test this hypothesis.

Detailed Description Text (85):

The conformations of the energy-minimized models of the compounds listed in Table 1 were relatively planar, with dihedral angles of approximately 4-18.degree. between the phenyl ring and quinazoline ring system. This conformation allows the compounds to fit more easily into the catalytic site of JAK3. All of the listed compounds contain a ring nitrogen (N1), which can form a hydrogen bond with NH of Leu905 in the hinge region of JAK3. When N1 is protonated, the NH can instead interact with the carbonyl group in Leu905 of JAK3. The presence of an OH group at the 4' position on the phenyl ring was anticipated to be particularly important for binding to the catalytic site of JAK3. WHI-P131 (estimated  $K_{sub.i} = 2.3 \text{ .}\mu\text{.M}$ ), WHI-P154 (estimated  $K_{sub.i} = 1.4 \text{ .}\mu\text{.M}$ ), WHI-P97 (estimated  $K_{sub.i} = 0.6 \text{ .}\mu\text{.M}$ ) shown in Table 1 were predicted to have favorable binding to JAK3 and potent JAK3 inhibitory activity because they contain a 4' OH group on the phenyl ring which can form a hydrogen bond with Asp967 of JAK3, contributing to enhanced binding. By comparison, the 2' OH group of WHI-P132 is not in the right orientation to interact with Asp967 and it probably would form an intramolecular hydrogen bond with the quinazoline ring nitrogen, which may contribute to a significantly lower affinity of WHI-P132 for the catalytic site of JAK3.

Detailed Description Text (91):

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4,5-Dimethoxy-2-nitrobenzoic acid (3) was treated with thionyl chloride and then reacted with ammonia to give 4,5-dimethoxy-2-nitrobenzamide (4) as described by F. Nomoto et al. Chem. Pharm. Bull., 1990, 38, 1591-1595. The nitro group in compound (4) was reduced with sodium borohydride in the presence of copper sulfate (see C. L. Thomas, Catalytic Processes and Proven Catalysts, Academic Press, New York (1970)) to give 4,5-dimethoxy-2-aminobenzamide (5) which was cyclized by refluxing with formic acid to give 6,7-dimethoxyquinazoline-4(3H)-one (6). Compound (6) was refluxed with phosphorus oxytrichloride to provide the common synthetic precursor (7).

Detailed Description Text (96):

4,5-Dimethoxy-2-nitrobenzamide 3: Yield 88.50%; mp 197.0-200.0.degree. C.; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 7.60 (s, 2H, --NH<sub>2</sub>), 7.57 (s, 1H, 6-H), 7.12 (s, 1H, 3-H), 3.90 (s, 3H, --OCH<sub>3</sub>), 3.87 (s, 3H, --OCH<sub>3</sub>); IR (KBr) 3454, 2840, 1670, 1512, 1274, 1227 cm<sup>-1</sup>; GC/MS m/z 226 (M<sup>+</sup>, 10), 178(99), 163(100), 135(51).

Detailed Description Text (99):

4-(3',5'-Dibromo-4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline WHI-P97: Yield 72.80%; mp>300.0.degree. C.; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 9.71 (s, 1H, --NH), 9.39 (s, 1H, --OH), 8.48 (s, 1H, 2-H), 8.07 (s, 2H, 2', 6'-H), 7.76 (s, 1H, 5-H), 7.17 (s, 1H, 8-H), 3.94 (s, 3H, --OCH<sub>3</sub>), 3.91 (s, 3H, --OCH<sub>3</sub>); IR (KBr) 3504, 3419, 2868, 1627, 1512, 1425, 1250, 1155 cm<sup>-1</sup>; GC/MS m/z 456 (M<sup>+</sup>+1, 54), 455 (M<sup>+</sup>, 100), 454 (M<sup>+</sup>-1, 78), 439 (M<sup>+</sup>--OH, 8), 376 (M<sup>+</sup>+1-Br, 10), 375 (M<sup>+</sup>-Br, 11), 360 (5); Anal. (C<sub>16</sub>H<sub>13</sub>Br<sub>2</sub>N<sub>3</sub>O<sub>3</sub>) C, H, N.

Detailed Description Text (102):

4-(4'-Hydroxyphenyl)-amino-6,7-dimethoxyquinazoline WHI-P131: Yield 84.29%; mp 245.0-248.0.degree. C.; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 11.21 (s, 1H, --NH), 9.70 (s, 1H, --OH), 8.74 (s, 1H, 2-H), 8.22 (s, 1H, 5-H), 7.40 (d, 2H, J=8.9 Hz, 2', 6'-H), 7.29 (s, 1H, 8-H), 6.85 (d, 2H, J=8.9 Hz, 3', 5'-H), 3.98 (s, 3H, --OCH<sub>3</sub>), 3.97 (s, 3H, --OCH<sub>3</sub>); IR (KBr) 3428, 2836, 1635, 1516, 1443, 1234 cm<sup>-1</sup>; GC/MS m/z 298 (M<sup>+</sup>+1, 100), 297 (M<sup>+</sup>, 27), 296 (M<sup>+</sup>-1, 12); Anal. (C<sub>16</sub>H<sub>15</sub>N<sub>3</sub>O<sub>3</sub>.HCl) C, H, N.

Detailed Description Text (103):

4-(2'-Hydroxyphenyl)-amino-6,7-dimethoxyquinazoline WHI-P132: Yield 82.49%; mp 255.0-258.0.degree. C.; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 9.78 (s, 1H, --NH), 9.29 (s, 1H, --OH), 8.33 (s, 1H, 2-H), 7.85 (s, 1H, 5-H), 7.41-6.83 (m, 4H, 3', 4', 5', 6'-H), 7.16 (s, 1H, 8-H), 3.93 (s, 3H, --OCH<sub>3</sub>), 3.92 (s, 3H, --OCH<sub>3</sub>); IR (KBr) 3500, 3425, 2833, 1625, 1512, 1456, 1251, 1068 cm<sup>-1</sup>; GC/MS m/z 298 (M<sup>+</sup>+1, 9), 297 (M<sup>+</sup>, 57), 281 (M<sup>+</sup>+1-OH, 23), 280 (M<sup>+</sup>-OH, 100); Anal. (C<sub>16</sub>H<sub>15</sub>N<sub>3</sub>O<sub>3</sub>.HCl) C, H, N.

Detailed Description Text (104):

4-(3'-Bromo-4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline WHI-P154: Yield 89.90%; mp 233.0-233.5.degree. C.; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 10.08 (s, 1H, --NH), 9.38 (s, 1H, --OH), 8.40 (s, 1H, 2-H), 7.89 (d, 1H, J<sub>2',6'</sub>=2.7 Hz, 2'-H), 7.75 (s, 1H, 5-H), 7.55 (dd, 1H, J<sub>5',6'</sub>=9.0 Hz, J<sub>2',6'</sub>=2.7 Hz, 6'-H), 7.14 (s, 1H, 8-H), 6.97 (d, 1H, J<sub>5',6'</sub>=9.0 Hz, 5'-H), 3.92 (s, 3H, --OCH<sub>3</sub>), 3.90 (s, 3H, --OCH<sub>3</sub>); IR (KBr) 3431, 2841, 1624, 1498, 1423, 1244 cm<sup>-1</sup>; GC/MS m/z 378 (M<sup>+</sup>+2, 91), 377 (M<sup>+</sup>+1, 37), 376 (M<sup>+</sup>, 100), 360 (M<sup>+</sup>+4, 298 (19), 282 (7); Anal. (C<sub>16</sub>H<sub>14</sub>BrN<sub>3</sub>O<sub>3</sub>.HCl) C, H, N.

Detailed Description Text (141):

Effects of Dimethoxy Quinoxalines on JAK-3 Activity

Detailed Description Text (173):

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Apr 22, 2003

DOCUMENT-IDENTIFIER: US 6552027 B2

TITLE: Quinazolines for treating brain tumorBrief Summary Text (2):

This invention relates to novel quinazoline derivatives effective to induce apoptosis of brain tumor cells. In particular, the invention includes novel hydroxy quinazoline derivatives having potent cytotoxicity against human brain tumor cells, including glioblastoma. The novel compounds of the invention further inhibit adhesion of brain tumor cells to extracellular matrix proteins and inhibit migration of brain tumor cells through the extracellular matrix, activities required for tumor metastases.

Brief Summary Text (7):

In a systematic effort to identify a cytotoxic agent with potent anti-tumor activity against glioblastoma cells, several hydroxy-substituted quinazoline-derivatives were synthesized and examined for their in vitro and in vivo effects on human glioblastoma cells. Novel hydroxy- and halo-hydroxy-quinazoline derivatives were found to exhibit potent cytotoxic activity against human glioblastoma cells at micromolar concentrations. Targeting of these compounds to the surface of brain tumor cells, for example, by conjugating hydroxy- and the halo-hydroxy compounds to a targeting moiety such as epidermal growth factor (EGF), further enhanced the cytotoxic activity (at nanomolar concentrations). The conjugate demonstrated more rapid and more potent anti-brain tumor activity, including apoptotic death of glioblastoma cells in vitro, significantly improved tumor-free survival in an in vivo SCID mouse glioblastoma xenograft model, inhibition of tumor cell adhesion to ECM proteins, and inhibition of tumor cell migration and invasion activity.

Brief Summary Text (8):

Accordingly, the present invention includes novel compounds and compositions having potent cytotoxic activity against brain tumor cells. Compositions of the invention contain an effective cytotoxic or inhibitory amount of a hydroxy-substituted quinozaline compound, more particularly of a hydroxy- or halo-hydroxy-substituted quinazoline derivative. The compounds of the invention include those having the following formula: ##STR1## where X is HN, R.sub.11 N, S, O, CH.sub.2, or R.sub.11 CH, and one or more of R.sub.1, R.sub.2, R.sub.3, R.sub.4, R.sub.5 is OH, SH, or NH.sub.2. Preferred embodiments include those where X is HN; R.sub.3 is OH; R.sub.2 and/or R.sub.4 is a halogen, preferably Br. In another preferred embodiment, one or more of R.sub.1 -R.sub.5 form a second ring fused to the phenyl ring, for example, forming a naphthyl ring and having at least one hydroxy substitution.

Brief Summary Text (9):

Preferred cytotoxic compounds of the invention include 4-(3'-Bromo-4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline[WHI-P154], 4-(4'-Hydroxylphenyl)-amino-6,7-dimethoxyquinazoline[WHI-P131], and 4-(2'-Hydroxy-naphthyl-3')-amino-6,7-dimethoxyquinazoline[WHI-P292].

Detailed Description Text (2):

The present invention includes novel hydroxy-substituted quinazoline derivatives having potent activity as cytotoxic agents against brain tumor cells, including glioblastoma cells. In addition, the hydroxy-substituted quinazoline compounds of



the invention are potent inhibitors of tumor cell adhesion and migration, activities required for tumor cell metastases.

Detailed Description Text (11):

The novel substituted quinazolines of the invention have the general structure represented by the following formula I: ##STR2## where X is selected from the group consisting of HN, R.sub.11 N, S, O, CH.sub.2, and R.sub.11 --CH. R.sub.11 is H, alkyl, having 1 to 4 carbon atoms, or acyl. Preferably, X is NH; and preferably R.sub.11 is H.

Detailed Description Text (17):

4-(3',5'-Dibromo-4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline[WHI- P971 ] ##STR4##

Detailed Description Text (21):

4-(4'-Hydroxyphenyl)-amino-6,7-dimethoxyquinazoline[WHI-P131] ##STR6##

Detailed Description Text (23):

4-(2'-Hydroxyphenyl)-amino-6,7-dimethoxyquinazoline[WHI-P132] ##STR7##

Detailed Description Text (25):

4-(3'-Bromo-4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline[WHI-P154] ##STR8##

Detailed Description Text (27):

4-(3'-Hydroxyphenyl)-amino-6,7-dimethoxyquinazoline[WHI-P180] ##STR9##

Detailed Description Text (29):

4-(3'-Chloro4'-Hydroxyphenyl)-amino-6,7-dimethoxyquinazoline[WHI-P971] ##STR10##

Detailed Description Text (37):

The Examples below further demonstrate the effectiveness of the hydroxy-substituted quinazoline compounds of the invention as inhibitors of brain tumor cell adhesion to extracellular matrix and of tumor cell migration. Each of the tested compounds having a hydroxy substituents on the phenyl ring demonstrated inhibitory activity against glioblastoma cell adhesion/migration. Particularly potent and useful inhibitory compounds include WHI-P154, WHI-P131, and WHI-P292.

Detailed Description Text (40):

Synthesis of Novel Hydroxy-Substituted Quinazoline Derivatives

Detailed Description Text (41):

The hydroxy-substituted quinazoline derivatives of the invention can be synthesized from a key starting material, 4-chloro-6,7-dimethoxyquinazoline, prepared using published procedures (Nomoto, et al., 1990, Chem. Pharm. Bull., 38:1591-1595; Thomas, C. L., 1970, Academic Press, New York N.Y., "I. Synthesis of quinazoline derivatives") as outlined below in Scheme 1 and as described more fully in the Examples below: ##STR12##

Detailed Description Text (45):

The term "conjugate" is meant to include a compound formed as a composite between two or more molecules. More specifically, in the present invention, the novel hydroxy-substituted quinazoline derivatives are bonded, for example, covalently bonded, to cell-specific targeting moieties forming a conjugate compound for efficient and specific delivery of the agent to a cell of interest.

Detailed Description Text (54):

To form the conjugates of the invention, targeting moieties are covalently bonded to sites on the hydroxy-substituted quinazoline compounds. The targeting moiety, which is often a polypeptide molecule, is bound to compounds of the invention at reactive sites, including NH.sub.2, SH, CHO, COOH, and the like. Specific linking

agents are used to link the compounds. Preferred linking agents are chosen according to the reactive site to which the targeting moiety is to be attached.

Detailed Description Text (77):

In addition, the compositions of the invention may be administered in combination with other anti-tumor therapies. In such combination therapy, the administered dose of the hydroxy-substituted quinazoline derivatives would be less than for single drug therapy.

Detailed Description Text (81):

Synthesis of Quinazoline Derivatives

Detailed Description Text (83):

The key starting material, 4-chloro-6,7-dimethoxyquinazoline, was prepared using published procedures (Nomoto, et al., 1990, Chem. Pharm. Bull., 38:1591-1595; Thomas, C. L., 1970, Academic Press, New York, N.Y., "I. Synthesis of quinazoline derivatives") as outlined below in Scheme 1: ##STR15##

Detailed Description Text (84):

Specifically, 4,5-dimethoxy-2-nitrobenzoic acid (compound 1) was treated with thionyl chloride to form acid chloride, followed by reacting with ammonia to yield 4,5-dimethoxy-2-nitrobenzamide (compound 2). Compound 2 was reduced with sodium borohydride in the presence of catalytic amounts of copper sulphate to give 4,5-dimethoxy-2-aminobenzamide (compound 3), which was directly refluxed with formic acid to yield 6,7-dimethoxyquinazoline-4(3H)-one (compound 4). Compound 4 was refluxed with phosphorus oxytrichloride to give 4-chloro-6,7-dimethoxyquinazoline (compound 5) in good yield.

Detailed Description Text (85):

Substituted quinazoline derivatives were prepared by the condensation of 4-chloro-6,7-dimethoxyquinazoline with substituted anilines as outlined below in Scheme 2: ##STR16##

Detailed Description Text (87):

As discussed above, the novel hydroxy-substituted quinazoline derivatives of the invention were created by reacting substituted anilines with the key starting material, 4-chloro-6,7-dimethoxyquinazoline. Each of the anilines to synthesize the compounds is shown in the table below.

Detailed Description Text (89):

Characterization of Substituted Quinazoline Derivatives

Detailed Description Text (90):

The substituted quinazoline derivatives were synthesized as described in Example 1 and characterized. Each structure is shown below, along with its identifying analytical test results. Proton and carbon Nuclear Magnetic Resonance (<sup>1</sup>H and <sup>13</sup>C NMR) spectra were recorded on a Mercury 2000 Varian spectrometer operating at 300 MHz and 75 MHz, respectively, using an automatic broad band probe. Unless otherwise noted, all NMR spectra were recorded in CDCl<sub>3</sub> at room temperature. <sup>1</sup>H chemical shifts are quoted in parts per million ( $\delta$ , in ppm) downfield from tetramethyl silane (TMS), which was used as an internal standard at 0 ppm and s, d, t, q, m designate singlet, doublet, triplet, quartet and multiplet, respectively. Melting points were determined using a Fisher-Johns melting apparatus and are uncorrected. UV spectra were recorded using a Beckmann Model # DU 7400 UV/V is spectrometer with a cell path length of 1 cm. Methanol was used as the solvent for the UV spectra. Fourier Transform Infrared spectra were recorded using an FT-Nicolet model Protege #460 instrument. The infrared spectra of the liquid samples were run as neat liquids using KBr discs. The KBr pellet method was used for all solid samples. The GC/mass spectrum analysis was conducted using a Hewlett-Packard GC/mass spectrometer model #6890 equipped with a mass ion detector

and Chem Station software. The temperature of the oven was steadily increased from 70.degree. C. to 250.degree. C. and the carrier gas was helium.

Detailed Description Text (92):

Cytotoxicity of Substituted Quinazoline Derivatives

Detailed Description Text (93):

The cytotoxicity of the substituted quinazoline derivative compounds against human glioblastoma cells was evaluated. The relative importance of particular substituent group on the compounds was also studied. The substituted quinazoline derivative compounds, prepared as described above for Example 1, were tested, along with DMSO and Genistein as controls.

Detailed Description Text (95):

The cytotoxicity assay of various compounds against human brain tumor cell lines was performed using the MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide) assay (Boehringer Mannheim Corp., Indianapolis, Ind.). Briefly, exponentially growing brain tumor cells were seeded into a 96-well plate at a density of 2.5.times.10.sup.4 cells/well and incubated for 36 hours at 37.degree. C. prior to drug exposure. On the day of treatment, culture medium was carefully aspirated from the wells and replaced with fresh medium containing the quinazoline compounds WHI-P79, WHI-P97, WHI-P111, WHI-P131, WHI-P132, WHI-P154, WHI-P180, WHI-P197, WHI-P258, unconjugated EGF, or EGF-P154, as well as the tyrosine kinase inhibitory isoflavone genistein (GEN) at concentrations ranging from 0.1 to 250 .mu.M. Triplicate wells were used for each treatment.

Detailed Description Text (105):

Those substituted quinazoline derivatives having an hydroxyl group on the aniline moiety demonstrated cytotoxic activity. Four compounds tested possessed a single hydroxyl group; at position 4 (WHI-P131), at position 2 (WHI-P132), at position 3 (WHI-P180), and at position 1 (WHI-P292). All four exhibited significant cytotoxicity, with the WHI-P180 (3-OH) compound demonstrating slightly stronger effects than the other two.

Detailed Description Text (109):

WHI-P154, 4-(3'-Bromo-4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline exhibited significant cytotoxicity against the U373 human glioblastoma cell line in 3 of 3 independent experiments with a mean (.+-SE) IC50 value of 167.4.+-26.9 .mu.M and a composite survival curve IC50 value of 158.5 .mu.M. In contrast, WHI-P79, a potent inhibitor of EGF-R quid Src family tyrosine kinases (Bos, et al., 1997, Clin. Cancer Res. 3:2099-2106 Fry, et al., 1994, Science (Washington, D.C.) 265:1093-1095) failed to cause any detectable cytotoxicity to U373 glioblastoma cells. Thus, the cytotoxicity of WHI-P154 to U373 cells cannot be explained by its tyrosine kinase inhibitory properties. This notion was further supported by the inability of the PTK inhibitor genistein (included as controls) to cause detectable cytotoxicity to U373 cells (IC50 value >250 .mu.M; FIG. 1A).

Detailed Description Text (116):

In an attempt to enhance the demonstrated anti-tumor activity of 4-(3'-Bromo-4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline (WHI-P154) against glioblastoma cells, by improving its targeting to and cellular uptake by glioblastoma cells, the compound was conjugated to recombinant human EGF, as described below.

Detailed Description Text (129):

The kinetics of uptake and cytotoxicity of the EGF-P154 conjugate in U373 glioblastoma cells were analyzed using immunofluorescence and confocal laser microscopy for following the internalized EGF-R and EGF-P154 molecules, as well as morphologic changes in treated cells. EGF-P154, similar to unconjugated EGF (not shown), was able to bind to and enter target glioblastoma cells via receptor-mediated endocytosis by inducing internalization of the EGF-R molecules. As shown

in FIGS. 3A-C, 3C', 3D and 3D', within 10 minutes after exposure to EGF-P154, the EGF-R/EGF-P154 complexes began being internalized, as determined by co-localization of the EGF-R (detected by anti-EGF-R antibody, green fluorescence) and EGF-P154 (detected by anti-P154 antibody, red fluorescence) in the cytoplasm of treated cells. By 30 minutes, the internalized EGF-R/EGF-P154 complexes were detected in the perinuclear region of the treated glioblastoma cells. In contrast, cells treated with unconjugated WHI-P154 alone (FIGS. 3B, 3B') did not reveal any detectable redistribution of the surface EGF-R or cytoplasmic staining with the anti-P154 antibody (red fluorescence). By 24 hours (but not at 6 or 12 hours), WHI-P154 molecules could also be detected in cells treated with unconjugated WHI-154 (FIGS. 4A, 4A', 4B, 4B'). Thus, conjugation of WHI-P154 to EGF resulted in increased uptake of this cytotoxic quinazoline derivative by EGF-R positive glioblastoma cells.

Detailed Description Text (145):

The conjugated quinazoline EGF-P154 significantly improved tumor-free survival in a dose-dependent fashion, when it was administered 24 hours after inoculation of tumor cells. FIGS. 7A and 7B show the tumor growth and tumor-free survival outcome of SCID mice treated with EGF-P154 (500 .mu.g/kg/day.times.10 days or 1 mg/kg/day.times.10 days), unconjugated EGF (1 mg/kg/day.times.10 days), unconjugated WHI-P154 (1 mg/kg/day.times.10 days), or PBS after inoculation with U373 glioblastoma cells.

Detailed Description Text (149):

Taken together, the findings of Examples 3-5 provide unprecedented evidence that the substituted quinazoline 3-bromo-4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline (WHI-P154) exhibits significant cytotoxicity against human glioblastoma cells and that its anti-tumor activity can be substantially enhanced by conjugation to EGF as a targeting molecule. Although WHI-P154 is a potent inhibitor of the EGF-R kinase as well as Src family tyrosine kinases, its cytotoxicity in glioblastoma cells cannot be attributed to its tyrosine kinase inhibitory properties alone, since 4-(3'-Bromophenyl)-amino-6,7-dimethoxyquinazoline (WHI-P79) with equally potent PTK inhibitory activity, failed to kill WHI-P154 sensitive glioblastoma cells. Similarly, several PTK inhibitors capable of killing human leukemia and breast cancer cells lacked detectable cytotoxicity against glioblastoma cells. Glioblastoma cells exposed to EGF-conjugated WHI-P154 underwent apoptosis. Although EGF was used to target WHI-P154 to glioblastoma cells in the present study, other biologic agents including different cytokines such as IGF and antibodies reactive with glioblastoma-associated antigens are also ted to be effective targeting molecules for this novel quinazoline derivative.

Detailed Description Text (151):

Substituted Quinazolines Inhibit Glioblastoma Cell Adhesion

Detailed Description Text (156):

In vitro adhesion assays were performed to (a) study the baseline adhesive properties of various glioblastoma cell lines and (b) evaluate the effects of quinazoline derivatives on the adhesive properties of glioblastoma cells. The plates for the adhesion assays were precoated with the extracellular matrix proteins laminin, fibronectin or type IV collagen (each at a final concentration of 1 .mu.g/ml in PBS) overnight at 4.degree. C. and dried. On the day of the experiment, the wells were rehydrated and blocked with 10% bovine serum albumin in PBS for 1 hour at room temperature and used for the adhesion assays, as described below.

Detailed Description Text (157):

To study the effects of quinazoline derivatives on glioblastoma cell adhesion, exponentially growing cells in DMEM were incubated with the compounds WHI-P79, WHI-P97, WHI-P31, WHI-P154, WHI-P258 or genistein at concentrations ranging from

1  $\mu$ M to 100  $\mu$ M for 16 hours in a humidified 5% CO<sub>2</sub> atmosphere. DMSO (0.1%) was included as a vehicle control. After treatment, cells were detached from the flasks with 0.05% trypsin (Life Technologies) resuspended in DMEM, incubated at 37.degree. C. for 2 hours to allow them to recover from the trypsinization stress and examined for their ability to adhere to plates precoated with ECM proteins.

Detailed Description Text (158):

In adhesion assays, cells were centrifuged, washed twice with serum-free DMEM, counted and resuspended in serum-free DMEM to a final concentration of 2.5.times.10<sup>5</sup> cells/ml. One hundred  $\mu$ l of the cell suspension containing 2.5.times.10<sup>4</sup> cells were added to each well and cells were allowed to adhere for 1 hour at 37.degree. C. in a humidified 5% CO<sub>2</sub> atmosphere. The adherent fraction was quantitated using MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) assays. In brief, after washing the wells, 10  $\mu$ l of MTT (0.5  $\mu$ g/ml final concentration) (Boehringer Mannheim Corp., Indianapolis, Ind.) was added to each well and the plates were incubated at 37.degree. C. for 4 hours to allow MTT to form formazan crystals by reacting with metabolically active cells. The formazan crystals were solubilized overnight at 37.degree. C. in a solution containing 10% SDS in 0.01 M HCl. The absorbance of each well was measured in a microplate reader (Labsystems) at 540 nm and a reference wavelength of 690 nm. To translate the OD<sub>540</sub> values into the number of cells in each well, the OD<sub>540</sub> values were compared to those on standard OD<sub>540</sub> -versus-cell number curves generated for each cell line. The adherent fractions of cells treated with quinazoline derivatives were compared to those of DMSO-treated control cells and the percent inhibition of adhesion was determined using the formula: ##EQU3##

Detailed Description Text (161):

As shown in FIG. 8, a significantly greater fraction of glioblastoma and medulloblastoma cells adhered to plates precoated with laminin, type IV collagen, or fibronectin than to uncoated or poly L-lysine-coated control plates. Of the four glioblastoma cell lines examined, U373 cells were the most adhesive. Therefore, U373 cells were used in subsequent experiments that were designed to examine the effects of various quinazoline derivatives on integrin-mediated glioblastoma cell adhesion.

Detailed Description Text (162):

As shown in FIGS. 9A-9D, the novel quinazoline derivative 4-(3'-Bromo-4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline (WHI-P154) (but not the unsubstituted parent compound WHI-P258) inhibited the adhesion of U373 cells to laminin-, fibronectin-, and collagen-coated plates in a dose-dependent fashion with mean IC<sub>50</sub> values of 29.8 $\pm$ .3.1  $\mu$ M (N=3) for adhesion to fibronectin-coated plates, 36.1 $\pm$ .3.5  $\mu$ M (N=3) for adhesion to laminin-coated plates, and 42.7 $\pm$ .2.5  $\mu$ M (N=3) for adhesion to collagen-coated plates. The 3'-bromo substitution on the phenyl ring likely contributes to the activity of WHI-P154 since 4-(4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline [WHI-P131] lacking this bromo substituent was less potent than WHI-P154 (all IC<sub>50</sub> values: >50  $\mu$ M). The 4'-hydroxyl substituent on the phenyl ring also contributed to the inhibitory activity of WHI-P154 since 4-(3'-Bromophenyl)-amino-6,7-dimethoxyquinazoline [WHI-P79] which differs from WHI-P154 only by the lack of the 4'-hydroxyl group on the phenyl ring, was less potent (all IC<sub>50</sub> values: >50  $\mu$ M). Introduction of a second bromo group at the 5' position of the phenyl ring did not result in improved inhibitory activity 4-(3', 5'-Dibromo-4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline [WHI-P97] was not more potent than WHI-P154.

Detailed Description Text (166):

To study the effects of quinazoline derivatives on EGF-stimulated cell adhesion, the trypsinized and recovered cells were incubated with varying concentrations ranging from 1  $\mu$ M to 50  $\mu$ M of quinazolines for 4 hours at 37.degree. C., then stimulated with 250 ng/ml of EGF and examined for their ability to adhere to poly-L-lysine coated plates.

Detailed Description Text (170):

Substituted Quinazolines Inhibit Glioblastoma Cell Invasion

Detailed Description Text (173):

On the day of the experiment, the coated inserts were rehydrated with 0.5 ml serum-free DMEM containing 0.1% bovine serum albumin for 1-2 hours. To study the effects of quinazoline derivatives on invasiveness of glioblastoma cells, exponentially growing cells were incubated overnight with WHI-P97, WHI-P131 and WHI-P154 at various concentrations ranging from 1 .mu.M to 50 .mu.M. The cells were trypsinized, washed twice with serum-free DMEM containing BSA, counted and resuspended at 1.times.10.sup.5 cells/ml. 0.5 ml cell suspension containing 5.times.10.sup.4 cells in a serum-free DMEM containing quinazoline compounds or vehicle was added to the Matrigel-coated and rehydrated filter inserts. Next, 750 .mu.l of NIH fibroblast conditioned medium was placed as a chemoattractant in 24-well plates and the inserts were placed in wells and incubated at 37.degree. C. for 48 hours. After the incubation period, the filter inserts were removed, the medium was decanted off and the cells on the top side of the filter that did not migrate were scraped off with a cotton-tipped applicator. The invasive cells that migrated to the lower side of the filter were fixed, stained with Hema-3 solutions and counted under microscope. Five to 10 random fields per filter were counted to determine the mean (.+-SE) values for the invasive fraction. The invasive fractions of cells treated with quinazoline derivatives were compared to those of DMSO treated control cells and the percent inhibition of invasiveness was determined using the formula: ##EQU4##

Detailed Description Text (178):

Substituted Quinazolines Inhibit Focal Adhesion Plaques and Actin Polymerization

Detailed Description Text (183):

Immunofluorescence was used to study the effects of quinazoline derivatives on the formation of focal adhesion plaques and polymerization of actin. Cells (obtained and maintained as described for Example 6) were plated on poly-L-lysine-coated glass-bottom 35 mm Petri dishes (Mattek Corp., Ashland, Mass.) or fibronectin-coated cover slips and maintained in DMEM supplemented with 10% FBS for 24 hrs. The medium was removed and the cells were washed twice with serum-free DMEM and incubated in the same medium for 16 hours. Following this serum starvation, cells were incubated with varying concentrations of WHI-P131, WHI-P154 or vehicle (0.1% DMSO) for 4-16 hours at 37.degree. C. and then stimulated either with 250 ng/ml of human recombinant EGF or 10% FBS for 15, 30, 60, 120 or 180 minutes at 37.degree. C. At the end of the EGF stimulation, cells were washed twice with PBS, fixed in 2% paraformaldehyde in PBS (pH 7.2), permeabilized and non-specific binding sites were blocked with 1.5% BSA and 0.1% triton X-100 in PBS for 30 minutes.

Detailed Description Text (187):

To evaluate the actin polymerization process, cells plated on poly-L-lysine-coated plates were first serum-starved to depolymerize the actin stress fibers. Subsequently, cells were stimulated with fetal bovine serum to induce de novo stress fiber formation. As shown in FIGS. 13A-C, a two-hour stimulation of serum-starved U373 cells with fetal bovine serum (10% v/v) resulted in a marked increase in polymerized actin stress fibers. Pretreatment of serum-starved U373 cells with WHI-P154 inhibited serum-induced actin polymerization (FIG. 13C). Similar results were obtained with WHI-P131 but not with the unsubstituted dimethoxy quinazoline compound WHI-P258 (data not shown).

Detailed Description Text (188):

In summary, the data provided in Examples 6-9 demonstrate the effectiveness of substituted quinazolines in the inhibition of glioblastoma cell adhesion and migration, key factors for tumor cell metastasis. The most potent inhibitory agents were WHI-P154 and WHI-P131. Both compounds inhibited adhesion and migration at

micromolar concentration.

Detailed Description Paragraph Table (2):

4-(3'-Bromophenyl)-amino-6,7-dimethoxyquinazoline [WHI-P79] ##STR27## yield 84.17%; m.p. 246.0-249.0.degree. C. UV(MeOH).lambda..sub.max : 217.0, 227.0, 252.0 nm; IR (KBr).nu..sub.max : 3409, 2836, 1632, 1512, 1443, 1243, 1068 cm.sup.-1 ; .sup.1 H NMR(DMSO-d.sub.6): .delta. 10.42(br, s, 1H, NH), 8.68(s, 1H, 2-H), 8.07-7.36(m, 5H, 5,2', 4', 5', 6'-H), 7.24(s, 1H), 8H), 3.98(s, 3H, --OCH.sub.3), 3.73(s, 3H, --OCH.sub.3); GC/MS m/z 361(M.sup.+ + 1, # 61.83), 360(M.sup.+ , 100), 359(M.sup.+ - 1, 63.52), 344(11.34), 222(10.87), 140(13.65). Anal. (C.sub.16 H.sub.14 BrN.sub.3 O.sub.2) C, H, N. 4-(3', 5'-Dibromo-4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline [WHI-P97] ##STR28## yield 72.80%; m.p. > 300.0.degree. C. UV (MeOH).lambda..sub.max : 208.0, 210.0, 245.0, 320.0 nm; IR(KBr).upsilon..sub.max : 3504(br), 3419, 2868, 1627, 1512, 1425, 1250, 1155 cm.sup.-1 ; .sup.1 H NMR(DMSO-d.sub.6): .delta. 9.71(s, 1H, --NH), 9.39(s, 1H, --OH), 8.48(s, 1H, 2-H), 8.07(s, 2H, 2', 6'-H), 7.76(s, 1H, 5-H), 7.17(s, 1H, 8-H), 3.94(s, 3H, --OCH.sub.3), 3.91(s, 3H, # --OCH.sub.3). GC/MS m/z 456(M.sup.+ + 1, 54.40), 455(M.sup.+ , 100.00), 454(M.sup.+ - 1, 78.01), 439(M.sup.+ --OH, 7.96), 376(M.sup.+ + 1-Br, 9.76), 375(M.sup.+ - Br, 10.91), 360(5.23). Anal. (C.sub.16 H.sub.13 Br.sub.2 N.sub.3 O.sub.3) C, H, N. 4-(3'-Bromo-4'-methylphenyl)-amino-6,7-dimethoxyquinazoline [WHI-P111] ##STR29## yield 82.22%; m.p. 225.0-228.degree. C. .sup.1 H NMR(DMSO-d.sub.6): .delta. 10.23(s, 1H, --NH), 8.62(s, 1H, 2-H), 8.06(D, 1h, j.sub.2',6' =2.1 Hz. 2'-H), 7.89(s, 1H, 5-H), 7.71(dd, 1H, J.sub.5',6' =8.7 Hz, J.sub.2',6' =2.1 Hz, 6'-H), 7.37(d, 1H, J.sub.5',6' =8.7 Hz, 5'-H, 7.21(s, 1H, 8-H), 3.96(s, 3H, --OCH.sub.3), 3.93(s, --OCH.sub.3). # UV(MeOH).lambda..sub.max (.epsilon): 204.0, 228.0, 255.0, 320.0 nm. IR(KBr).upsilon..sub.max : 3431, 3248, 2835, 1633, 1517, 1441, 1281, 1155 cm.sup.-1. GC/MS m/z 375(M.sup.+ + 1, 76.76), 374(M.sup.+ , 100.00), 373(M.sup.+ - 1, 76.91), 358(M.sup.+ + 1-OH, 11.15), 357(1.42), 356(6.31). Anal. (C.sub.17 H.sub.16 BrN.sub.3 O.sub.2 HCl) C, H, N. 4-(4'-Hydroxyphenyl)-amino-6,7-dimethoxyquinazoline [WHI-P131] ##STR30## yield 84.29%; m.p. 245.0-248.0.degree. C. UV(MeOH).lambda..sub.max : 203.0, 222.0, 251.0, 320.0 nm; IR (KBr).upsilon..sub.max : 3428, 2836, 1635, 1516, 1443, 1234 cm.sup.-1 ; .sup.1 H NMR(DMSO-d.sub.6): .delta. 11.21(s, 1H, --NH), 9.70(s, 1H, --OH), 8.74(s, 1H)2-H), 8.22(s, 1H, 5-H), 7.40(d, 2H, J=8.9 Hz, 2', 6'-H), 7.29(s, 1H, 8-H), 6.85(d, 2H, J=8.9 Hz, 3', 5'-H), 3.98(s, 3H, # --OCH.sub.3)3.97(s,3H,--)CH.sub.3). GC/MS m/z 298(M.sup.+ + 1, 100.00), 297(M.sup.+ , 26.56), 296(M.sup.+ - 1, 12.46). Anal. (C.sub.16 H.sub.15 N.sub.3 O.sub.3 HCl) C, H, N. 4-(2'-Hydroxyphenyl)-amino-6,7-dimethoxyquinazoline [WHI-P132] ##STR31## yield 82.49%; m.p. 255.0-258.0.degree. C. .sup.1 H NMR(DMSO-d.sub.6): .delta. 9.78(s, 1H, --NH), 9.29(s, 1H, --OH), 8.33(s, 1H, 2-H), 7.85(s, 1H, 5-H), 7.41-6.83(m, 4H, 3', 4', 5', 6'-H), 7.16(s, 1H, 8-H), 3.93(s, 3H, --OCH.sub.3), 3.92(s, 3H, --OCH.sub.3). UV(mEoh).lambda..sub.max (.epsilon): 203.0, 224.0, 245.0, 335.0 nm. IR(KBr).upsilon..sub.max : 3500(br), 3425, 2833, 1625, 1512, 1456, # 1251, 1068 cm.sup.-1. GC/MS m/z 298(M.sup.+ + 1, 8.91), 297(M.sup.+ , 56.64), 281(M.sup.+ + 1-OH, 23.47), 280(M.sup.+ - OH, 100.00). Anal. (C.sub.16 H.sub.15 N.sub.3 O.sub.3 HCl) C, H, N. 4-(3'-Bromo-4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline [WHI-P154] ##STR32## yield 89.90%; m.p. 233.0-233.5.degree. C. UV(MeOH).lambda..sub.max : 203.0, 222.0, 250.0, 335.0 nm; IR(KBr).upsilon..sub.max : 3431 br, 2841, 1624, 1498, 1423, 1244 cm.sup.-1 ; .sup.1 H NMR(DMSO- d.sub.6): .delta. 10.09(s, 1H, --NH), 9.38(s, 1H, --OH), 8.40(s, 1H, 2-H), 7.89(d, 1H, J.sub.2', 5' =2.7 Hz, 2'-H), 7.75(s, 1H, 5-H), # 7.55(dd, 1H, J.sub.5',6' =9.0 Hz, J.sub.2',6' =2.7 Hz, 6'-H), 7.14(s, 1H, 8-H), 6.97(s, 1H, J.sub.5',6' = 9.0 Hz, 5'H), 3.92(s, 3H, --OCH.sub.3), 3.90(s, 3H, --OCH.sub.3). GC/MS m/z 378(M.sup.+ + 2, 90.68), 377(M.sup.+ + 1, 37.49), 376(M.sup.+ , 100.00), 360(M.sup.+ , 3.63), 298(18.86), 282(6.65). Anal. # (C.sub.16 H.sub.14 N.sub.3 O.sub.3 HCl) C, H, N. 4-(3'-Hydroxyphenyl)-amino-6,7-dimethoxyquinazoline [WHI-P180] ##STR33## yield 71.55%; m.p. 256.0-258.0.degree. C. .sup.1 H NMR(DMSO-d.sub.6): .delta. 9.41(s, 1H, --NH), 9.36(s, 1H, --OH), 8.46(s, 1H, 2- H), 7.84(s, 1H, 5-H), 7.84-6.50(m, 4H, 2', 4', 5', 6'-H), 7.20(s, 1H, 8-H), 3.96(s, 3H, --OCH.sub.3), 3.93(s, 3H, --OCH.sub.3). UV(MeOH).lambda..sub.max (.epsilon): 204.0, 224.0, 252.0, 335.0 nm. # IR(DBr).upsilon..sub.max : 3394, 2836, 1626, 1508, 1429,

h e b b g e e e f c e

e ge

1251 cm.<sup>sup.1</sup>. GM/MS m/z: 297(M.<sup>sup.+</sup>, 61.89), 296(M.<sup>sup.+</sup>, 61.89), 296(M.<sup>sup.+</sup> - 1, 100.00), 280(M.<sup>sup.+</sup> -OH, 13.63). Anal. (C.<sub>sub.16</sub> H.<sub>sub.15</sub> N.<sub>sub.3</sub> O.<sub>sub.3</sub>.HCl) C, H, N. 4-(3'-Chloro-4'-Hydroxylphenyl)-amino-6,7-dimethoxyquinazoline [WHI-P197] ##STR34## yield 84.14%; m.p. 245.0.degree. C. (dec). <sup>sup.1</sup> H NMR(DMSO-d.<sub>sub.6</sub>): .delta. 10.00(s, 1H, --NH), 9.37(s, 1H, --OH), 8.41(s, 1H, 2-H), 7.78(s, 1H, 5-H), 7.49(s, 1H, J.<sub>sub.2'</sub>, 6' =2.7Hz, 2'-H), 7.55(dd, 1H, J.<sub>sub.5'</sub>, 6' =0.0 Hz, J.<sub>sub.2'</sub>, 6' =2.7 Hz., 6'-H), 7.16(s, 1H, 8-H), 6.97(d, 1H, J.<sub>sub.5'</sub>, 6' =9.0 Hz, 5'-H), 3.93(s, 3H, --OCH.<sub>sub.3</sub>), # 3.91(s, 3H, --OCH.<sub>sub.3</sub>). UV(MeOH).lambda.<sub>sub.max</sub> (.epsilon.<sub>sub.1</sub>): 209.0, 224.0, 249.0, 330.0 nm. IR(KBr).upsilon.<sub>sub.max</sub> : 3448, 2842, 1623, 1506, 1423, 1241 cm.<sup>sup.-1</sup>. GC/MS m/z: 341(M.<sup>sup.+</sup>, 100.00), 326(M.<sup>sup.+</sup> - CH.<sub>sub.3</sub>, 98.50), 310(M.<sup>sup.+</sup> - OCH.<sub>sub.3</sub>, 12.5), 295(9.0), 189(13.5), 155(13.8). Anal. (C.<sub>sub.16</sub> H.<sub>sub.14</sub> Cl.<sub>sub.1</sub> N.<sub>sub.3</sub> O.<sub>sub.3</sub>.HCl) C, H, N. 4-(phenyl)-amino-6,7-dimethoxyquinazoline [WHI-P258] ##STR35## yield 88.6%; m.p. 258.0-260.0.degree. C. <sup>sup.1</sup> H NMR(DMSO-d.<sub>sub.6</sub>): .delta. 11.41(s, 1H, --NH), 8.82(s, 1H, 2-H), 8.32(s, 1H, 5-H), 7.70-7.33(m, 5H, 2', 3', 4', 5', 6'-H), 7.36(s, 1H, 8H), 4.02(s, 3H, --OCH.<sub>sub.3</sub>), 4.00(s, 3H, --OCH.<sub>sub.3</sub>), 4.00(s, 3H, --OCH.<sub>sub.3</sub>). UV (MeOH).lambda.<sub>sub.max</sub> (.epsilon.<sub>sub.1</sub>): 210.0, 234.0, 330.0 nm. # IR (KBr).upsilon.<sub>sub.max</sub> : 2852, 1627, 1509, 1434, 1248 cm.<sup>sup.-1</sup>. GC/MS m/z 282 (M.<sup>sup.+</sup> + 1, 10.50), 281(M.<sup>sup.+</sup>, 55.00), 280(M.<sup>sup.+</sup> - 1, 100.00), 264(16.00), 207(8.50). Anal. (C.<sub>sub.16</sub> H.<sub>sub.15</sub> N.<sub>sub.3</sub> O.<sub>sub.2</sub>) C, H, N. 4-(2'-Hydroxy-naphthyl-3'-amino-6,7-dimethoxyquinazoline [WHI-P292]. ##STR36## Yield 87.41%; m.p. 277.0-279.0.degree. C., IR(KBr).delta.<sub>sub.max</sub> : 3479, 3386, 3036, 2901, 1632, 1581, 1504, 1437, 1281 cm.<sup>sup.-1</sup>. <sup>sup.1</sup> H NMR(DMSO-d.<sub>sub.6</sub>): .delta. 11.38(s, 1H, --NH), 10.35(s, 1H, --OH), 8.73(s, 1H, 2-H), 8.25(s, 1H, 5-H), 7.93-7.30(m, 6H, 1', 4', 5', 6', 7', 8'-H), 7.37(s, 1H, 8H), 4.00(s, 6H, --OCH.<sub>sub.3</sub>). GC/MS m/a: 281 (41.0), 253(11.0), 207(100.0). Anal. (C.<sub>sub.20</sub> H.<sub>sub.17</sub> N.<sub>sub.3</sub> O.<sub>sub.3</sub>.HCl) C, H, N.

Detailed Description Paragraph Table (3):

Quinazoline Derivatives Identity of Substituents ##STR37## WHI-P79 WHI-P97 WHI-P111 WHI-P131 WHI-P132 WHI-P154 WHI-P180 WHI-P197 WHI-258 WHI-292 3-Br 3-Br, 5-Br, 4-OH 3-Br, 4-CH.<sub>sub.3</sub> 4-OH 2-OH 3-Br, 4-OH 3-OH 3-Cl, 4-OH H 1-OH Naphthyl

Other Reference Publication (2):

Budesinsky, Z., et al., "A New Synthesis of the Quinazoline Nucleus", Collection of Czechoslovak Chemical Communications, vol. 37, No. 8, pp. 2779-2785 (Aug. 1972).

Other Reference Publication (6):

Higashino, T. et al., "Reactions of the anion of quinazoline Reissert compound (3-benzoyl-3, 4-dihydro-4-quinazolinecarbon itrile) with electrophiles", Chemical & Pharmaceutical Bulletin, vol. 33, No. 3, pp. 950-961 (Mar. 1985).

Other Reference Publication (10):

Miyashita, A. et al., "An Approach to the Synthesis of a Papaverine Analogue Containing a Quinazoline Ring System", Heterocycles, vol. 40, No. 2, pp. 653-660 (1995).

Other Reference Publication (11):

Myers et al., "The Preparation and SAR of 4-(Anilino), 4-(Phenoxy), and 4-(Thiophenoxy)-Quinazolines: Inhibitors of p56lck and EGF-R Tyrosine Kinase Activity", Bioorganic & Medicinal Chemistry Letters, vol. 7, No. 4, pp. 417-420 (Feb. 18, 1997).

Other Reference Publication (12):

Narla, R. et al., "4-(3'-Bromo-4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline: A Novel Quinazoline Derivative with Potent Cytotoxic Activity Against Human Glioblastoma Cells", Clinical Cancer Research, vol. 4, pp. 1405-1414 (Jun. 1998).

Other Reference Publication (13):

Nomoto, Y. et al., "Studies on Cardiogenic Agents. I. Synthesis of some Quinazoline



Derivatives", Chemical and Pharmaceutical Bulletin, vol. 38, No. 6, pp. 1591-1595 (1990).

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L5: Entry 7 of 18

File: USPT

Mar 19, 2002

DOCUMENT-IDENTIFIER: US 6358962 B2

TITLE: 6,7-Dimethoxyquinazolines and therapeutic use thereof

Abstract Text (1):

Quinazoline compounds and methods for the treatment of cancer and for the treatment of allergic reactions.

Brief Summary Text (2):

This application relates to quinazoline compounds, compositions and therapeutic methods for the treatment of cancers and treatment of allergic disorders by administering quinazoline compounds.

Brief Summary Text (4):

Quinazoline compounds have been suggested as useful compounds in the treatment of cell growth and differentiation characterized by activity of the human epidermal growth factor receptor type2 (HER2). See, for example, Myers et.al., U.S. Pat. No. 5,721,237. Some quinazoline derivatives have been suggested as useful as anti-cancer agents for the treatment of specific receptor tyrosine kinase-expressing cancers, especially those expressing epithelial growth factor (EGF) receptor tyrosine kinase. See, for example, Barker et. al., U.S. Pat. No. 5,457,105. It is generally taught that quinazolines exert their anti-tumor effects via tyrosine kinase inhibition. However, while some quinazoline compounds inhibit the growth of brain tumor cells, others with equally potent tyrosine kinase inhibitory activity fail to do so (Naria et.al., 1998, Clin. Cancer Res. 4:1405-1414; Naria et.al., 1998, Clin. Cancer Res. 4:2463-2471).

Brief Summary Text (5):

Several tumors expressing EGF receptors are not killed by quinazoline compounds, whereas some tumors not expressing EGF receptors are. Thus, the cytotoxic activity of quinazoline compounds cannot be attributed to the compound's tyrosine kinase inhibitory activity, and particularly not to the compound's ability to inhibit EGF receptor tyrosine kinase. A chemical structure-activity relationship determining the anti-cancer activity of quinazoline derivatives has not been established.

Brief Summary Text (6):

Novel quinazoline compounds may provide potent new therapeutic molecules for the treatment of disorders such as cancers. Methods of using both known and novel quinazoline compounds that employ an understanding of structure-function relationships are needed.

Brief Summary Text (8):

A series of quinazoline compounds were synthesized and analyzed for therapeutic activities, including anticancer activities, particularly against EGR receptor-negative leukemias. Specific quinazoline compounds of the invention were found to possess potent and specific tyrosine kinase inhibitory activities affecting cell proliferation and survival. Quinazoline compounds of the invention are demonstrated as useful for the treatment of specific tumors, including breast tumors, brain tumors, and leukemias, particularly EGF receptor-negative leukemias, and to be particularly useful in the treatment of multi-drug resistant leukemias.

Brief Summary Text (9):

The invention provides novel quinazoline compounds of formula I as disclosed below, as well as therapeutic methods utilizing these compounds.

Drawing Description Text (2):

FIGS. 1A-1C are graphs showing cytotoxic activity of fluoro-substituted dimethoxy quinazoline compounds (F-dmQ) against leukemic NALM-6 cells.

Drawing Description Text (8):

FIGS. 7A and 7B are bar graphs showing the anti-invasive activity of fluoro-substituted quinazoline compounds (F-dmQ) against glioblastoma U373 and breast cancer MDA-MB-231 cells.

Drawing Description Text (11):

FIGS. 10A-10C are graphs showing the inhibition of cancer cell growth in vivo by the quinazolines of the invention.

Detailed Description Text (3):

The terms "quinazoline", "quinazoline compound", and "quinazoline derivative" are used interchangeably in this application to mean compounds of formula I. All scientific and technical terms used in this application have meanings commonly used in the art unless otherwise specified. As used in this application, the following words or phrases have the meanings specified.

Detailed Description Text (6):

The term "conjugate" means a compound formed as a composite between two or more molecules. More specifically, in the present invention, the quinazoline derivative is bonded, for example, covalently bonded, to cell-specific targeting moieties forming a conjugate compound for efficient and specific delivery of the agent to a cell of interest. The phrase "targeting moiety" means a molecule which serves to deliver the compound of the invention to a specific site for the desired activity. Targeting moieties include, for example, molecules that specifically bind molecules on a specific cell surface. Such targeting moieties useful in the invention include anti-cell surface antigen antibodies. Cytokines, including interleukins and factors such as granulocyte/macrophage stimulating factor (GMCSF) are also specific targeting moieties, known to bind to specific cells expressing high levels of their receptors.

Detailed Description Text (11):

Compounds of the invention include quinazolines having the formula: ##STR1##

Detailed Description Text (23):

Additional preferred quinazoline compounds useful in the treatment of tumors are described more fully below and particularly in the Examples. These include:

Detailed Description Text (54):

The quinazoline compounds of the invention can be formulated as pharmaceutical compositions and administered to a mammalian host, such as a human patient in a variety of forms adapted to the chosen route of administration, i.e., orally or parenterally, by intravenous, intramuscular, topical or subcutaneous routes.

Detailed Description Text (55):

Thus, quinazoline compounds of the invention may be systemically administered, e.g., orally, in combination with a pharmaceutically acceptable vehicle such as an inert diluent or an assimilable edible carrier, or by inhalation or insufflation. They may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets, or may be incorporated directly with the food of the patient's diet. For oral therapeutic administration, the quinazoline compounds may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. The

quinazoline compounds may be combined with a fine inert powdered carrier and inhaled by the subject or insufflated. Such compositions and preparations should contain at least 0.1% quinazoline compounds. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 60% of the weight of a given unit dosage form. The amount of quinazoline compounds in such therapeutically useful compositions is such that an effective dosage level will be obtained.

Detailed Description Text (56):

The tablets, troches, pills, capsules, and the like may also contain the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the quinazoline compounds may be incorporated into sustained-release preparations and devices.

Detailed Description Text (57):

The quinazoline compounds may also be administered intravenously or intraperitoneally by infusion or injection. Solutions of the quinazoline compounds can be prepared in water, optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

Detailed Description Text (58):

The pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions or dispersions or sterile powders comprising the quinazoline compounds which are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. In all cases, the ultimate dosage form must be sterile, fluid and stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions or by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, buffers or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Detailed Description Text (59):

Sterile injectable solutions are prepared by incorporating the quinazoline compounds in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions,

the preferred methods of preparation are vacuum drying and the freeze drying techniques, which yield a powder of the active ingredient plus any additional desired ingredient present in the previously sterile-filtered solutions.

Detailed Description Text (60):

For topical administration, the quinazoline compounds may be applied in pure form, i.e., when they are liquids. However, it will generally be desirable to administer them to the skin as compositions or formulations, in combination with a dermatologically acceptable carrier, which may be a solid or a liquid.

Detailed Description Text (61):

Useful solid carriers include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina and the like. Other solid carriers include nontoxic polymeric nanoparticles or microparticles. Useful liquid carriers include water, alcohols or glycols or water-alcohol/glycol blends, in which the quinazoline compounds can be dissolved or dispersed at effective levels, optionally with the aid of non-toxic surfactants. Adjuvants such as fragrances and additional antimicrobial agents can be added to optimize the properties for a given use. The resultant liquid compositions can be applied from absorbent pads, used to impregnate bandages and other dressings, or sprayed onto the affected area using pump-type or aerosol sprayers.

Detailed Description Text (63):

Examples of useful dermatological compositions which can be used to deliver the quinazoline compounds to the skin are known to the art; for example, see Jacquet et al. (U.S. Pat. No. 4,608,392), Geria (U.S. Pat. No. 4,992,478), Smith et al. (U.S. Pat. No. 4,559,157) and Wortzman (U.S. Pat. No. 4,820,508).

Detailed Description Text (65):

Generally, the concentration of the quinazoline compounds in a liquid composition, such as a lotion, will be from about 0.1-25 wt-%, preferably from about 0.5-10 wt-%. The concentration in a semi-solid or solid composition such as a gel or a powder will be about 0.1-5 wt-%, preferably about 0.5-2.5 wt-%.

Detailed Description Text (66):

The amount of the quinazoline compounds required for use in treatment will vary not only with the particular salt selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or clinician.

Detailed Description Text (68):

The quinazoline compounds are conveniently administered in unit dosage form; for example, containing 5 to 1000 mg, conveniently 10 to 750 mg, most conveniently, 50 to 500 mg of active ingredient per unit dosage form.

Detailed Description Text (69):

Ideally, the quinazoline compounds should be administered to achieve peak plasma concentrations of from about 0.5 to about 75  $\mu\text{M}$ , preferably, about 1 to 50  $\mu\text{M}$ , most preferably, about 2 to about 30  $\mu\text{M}$ . This may be achieved, for example, by the intravenous injection of a 0.05 to 5% solution of the quinazoline compounds, optionally in saline, or orally administered as a bolus containing about 1-100 mg of the quinazoline compounds. Desirable blood levels may be maintained by continuous infusion to provide about 0.01-5.0 mg/kg/hr or by intermittent infusions containing about 0.4-15 mg/kg of the quinazoline compounds.

Detailed Description Text (70):

The quinazoline compounds may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations; such as, multiple

inhalations from an insufflator or by application of a plurality of drops into the eye.

Detailed Description Text (71):  
Targeting Quinazolines to Cells

Detailed Description Text (72):  
In a preferred embodiment, the quinazoline compound is targeted to cells where treatment is desired, for example, to leukemia cells, to breast cells, or to other tumor cells. The compound is targeted to the desired cell by conjugation to a targeting moiety that specifically binds the desired cell, thereby directing administration of a conjugated molecule. Useful targeting moieties are ligands which specifically bind cell antigens or cell surface ligands, for example, antibodies against the B cell antigen, CD19 (such as B43) and the like.

Detailed Description Text (73):  
To form the conjugates of the invention, targeting moieties are covalently bonded to sites on the quinazoline compound. The targeting moiety, which is often a polypeptide molecule, is bound to compounds of the invention at reactive sites, including NH.sub.2, SH, CHO, COOH, and the like. Specific linking agents are used to join the compounds. Preferred linking agents are chosen according to the reactive site to which the targeting moiety is to be attached.

Detailed Description Text (75):  
Administration of Quinazolines

Detailed Description Text (76):  
According to the invention, quinazoline compounds may be administered prophylactically, i.e., prior to onset the pathological condition, or the quinazoline compounds may be administered after onset of the reaction, or at both times.

Detailed Description Text (80):  
Synthesis of Quinazoline Derivatives

Detailed Description Text (82):  
The key starting material, 4-chloro-6,7-dimethoxyquinazoline, was prepared according to published procedures (Nomoto, et al., 1990, Chem. Pharm. Bull., 38:1591-1595; Thomas, C. L., 1970, IN:Catalytic Processes and Proven Catalysts, Academic Press, New York, N.Y.) as outlined below in Scheme 1. Specifically, 4,5dimethoxy-2-nitrobenzoic acid (compound 1) was treated with thionyl chloride to form acid chloride, followed by reacting with ammonia to yield 4,5-dimethoxy-2-nitrobenzamide (compound 2). Compound 2 was reduced with sodium borohydride in the presence of catalytic amounts of copper sulphate to give 4,5-dimethoxy-2-aminobenzamide (compound 3), which was directly refluxed with formic acid to yield 6,7-dimethoxyquinazoline-4(3H)-one (compound 4). Compound 4 was refluxed with phosphorus oxytrichloride to give 4-chloro-6,7-dimethoxyquinazoline (compound 5) in good yield. ##STR4##

Detailed Description Text (83):  
Substituted quinazoline derivatives were prepared by the condensation of 4-chloro-6,7-dimethoxyquinazoline with substituted anilines as outlined below in Scheme 2: ##STR5##

Detailed Description Text (85):  
As discussed above, the novel hydroxy-substituted quinazoline derivatives of the invention were created by reacting the appropriate substituted anilines with the key starting material, 4-chloro-6,7-dimethoxyquinazoline.

Detailed Description Text (89):

Bromine Substituted Quinazoline CompoundsDetailed Description Text (90):

Bromine substituted quinazoline derivatives were synthesized and characterized as discussed above in Example 1. The structures and physical data are shown below:

Detailed Description Text (93):

4-(3',5'-Dibromo-4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline (HI-P97). Yield 72.80%; m.p. >300.0.degree. C. .sup.1 H NMR(DMSO-d.sub.6): .delta. 9.71(s, 1H, --NH), 9.39(s, 1H, --OH), 8.48(s, 1H, 2-H), 8.07(s, 2H, 2',6-H), 7.76(s, 1H, 5-H), 7.17(s, 1H, 8-H), 3.94(s, 3H, --OCH.sub.3), 3.91(s, 3H, --OCH.sub.3). UV(MeOH): 208.0, 210.0, 245.0, 320.0 nm; IR(KBr).nu..sub.max : 3504(br), 3419, 2868, 1627, 1512, 1425, 1250, 1155 cm.sup.-1 ; GC/MS m/z 456(M.sup.+ +1, 54.40), 455(M.sup.+ , 100.00), 454(M.sup.+ -1, 78.01), 439(M.sup.+ --OH, 7.96), 376(M.sup.+ +1--Br, 9.76), 375(M.sup.+ --Br, 10.91), 360(5.23). Anal. (C.sub.16 H.sub.13 Br.sub.2 N.sub.3 O.sub.3) C, H, N.

Detailed Description Text (98):

4-(3'-Bromo-4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline (HI-P154): Yield 89.90%; m.p. 233.0-233.5.degree. C. .sup.1 H NMR(DMSO-d.sub.6): .delta. 10.08(s, 1H, --NH), 9.38(s, 1H, --OH), 8.40(s, 1H, 2-H), 7.89(d, 1H, J.sub.2',6' =2.7 Hz, 2'-H), 7.75(s, 1H, 5-H), 7.55(dd, 1H, J.sub.5',6' =9.0 Hz, J.sub.2',6' =2.7Hz, 6'-H), 7.14(s, 1H, 8-H), 6.97(d, 1H, J.sub.5',6' =9.0Hz, 5'-H), 3.92(s, 3H, --OCH.sub.3), 3.90(s, 3H, --OCH.sub.3). UV(MeOH): 203.0, 222.0, 250.0, 335.0 nm. IR (KBr).nu..sub.max : 3431(br), 2841, 1624, 1498, 1423, 1244 cm.sup.-1. GC/MS m/z 378 (M.sup.+ +2, 90.68), 377(M.sup.+ +1, 37.49), 376(M.sup.+ , 100.00), 360(M.sup.+ , 3.63), 298(18.86), 282 (6.65). Anal. (C.sub.16 H.sub.14 BrN.sub.3 O.sub.3.HCl) C, H, N.

Detailed Description Text (113):Chlorine Substituted Quinazoline CompoundsDetailed Description Text (114):

Chlorine substituted quinazoline derivatives were synthesized and characterized as discussed above in Example 1. The structures and physical data are shown below:

Detailed Description Text (118):

4-(3'-Chloro-4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline (HI-P197). Yield 84.14%; m.p. 245.0.degree. C. (dec). .sup.1 H NMR(DMSO-d.sub.6): .delta. 10.00(s, 1H, --NH), 9.37(s, 1H, --OH), 8.41(s, 1H, 2-H), 7.78(s, 1H, 5-H), 7.49(d, 1H, J.sub.2',5' =2.7 Hz, 2-H), 7.55(dd, 1H, J.sub.5',6' =9.0 Hz, J.sub.2',6' =2.7 Hz, 6'-H), 7.16(s, 1H, 8-H), 6.97(d, 1H, J.sub.5',6' =9.0 Hz, 5'-H), 3.93(s, 3H, --OCH.sub.3), 3.91(s, 3H, --OCH.sub.3). UV(MeOH): 209.0, 224.0, 249.0, 330.0 nm. IR (KBr).nu..sub.max : 3448, 2842, 1623, 1506, 1423, 1241 cm.sup.-1. GC/MX m/z: 341 (M.sup.+ , 100.00), 326(M.sup.+ --CH.sub.3, 98.50), 310(M.sup.+ --OCH.sub.3, 12.5), 295(9.0.), 189(13.5), 155(13.8). Found: C, 521.35; H, 4.16; Cl, 19.15; N, 11.39. C.sub.16 H.sub.14 ClN.sub.3 O.sub.3. HCl requires: C, 52.32; H, 4.09; Cl, 19.07; N, 11.44%.

Detailed Description Text (121):

4-(4'-Hydroxyl-2'-chlorophenyl)-amino-6,7-dimethoxy-quinazoline (HI-P278) Yield 81.44%; m.p. 245.0-247.0.degree. C. .sup.1 H NMR(DMSO-d.sub.6): .delta. 11.39(s, 1H, --NH), 10.30(s, 1H, --OH), 8.75(s, 1H, 2-H), 8.24(s, 1H, 5-H), 7.38-6.85(m, 3H, 3',5',6'-H), 7.37(s, 1H, 8H), 3.98(s, 3H, --OCH.sub.3), 3.96(s, 3H, --OCH.sub.3). UV (MeOH): 222.0, 234.0, 239.0, 245.0, 254.0, 348.0 nm. IR(KBr).nu..sub.max : 3448, 3242, 3144, 3025, 2917, 2834, 1638, 1591, 1514, 1437, 1365, 1277, 1209 cm.sup.-1. GC/MS m/z: 332(M.sup.+ +1, 5.00), 331(M.sup.+ ,17.00), 330(M.sup.+ -1, 5.00), 297 (17.00), 296(100.00), 281(18.00), 280(29.00), 253(9.00). Found: C, 52.17; H, 4.06; N, 11.32. C.sub.16 H.sub.14 ClN.sub.3 O.sub.3. HCl requires: C, 52.32; H, 4.01; N, 11.44%.

Detailed Description Text (124):Iodine Substituted Quinazoline CompoundsDetailed Description Text (125):

Iodine substituted quinazoline derivatives were synthesized as discussed above in Example 1, and analyzed. The structures and physical data are shown below:

Detailed Description Text (126):Iodine Substituted Quinazoline CompoundsDetailed Description Text (129):

4-(4'-Hydroxy-3,5-diiodophenyl)-amino-6,7-dimethoxy-quinazoline (HI-P294: Yield 77.47%; m.p. 259.0-260.0.degree. C. .sup.1 H NMR(DMSO-d.sub.6): .delta. 11.13(s, 1H, NH), 9.73(s, 1H, --OH), 8.87(s, 1H, 2-H), 8.16(s, 1H, 5-H), 8.09(s, 2H, 2',6'-H), 7.28(s, 1H, 8H), 3.98(s, 6H, --OCH.sub.3). UV(MeOH).lambda..sub.max (.epsilon.): 217.0, 227.0, 252.0 nm. IR(KBr).nu..sub.max : 3457, 3201, 2934, 2832, 2566, 1629, 1562, 1521, 1439, 1275, 1075 cm.sup.-1. GC/MS m/z: GC/MS m/z 422 (M.sup.+ -I,33.53), 405(7.50), 281(86.67), 221 (51.80), 207(91.30). Found: C, 32.60; H, 2.50; N, 6.92. C.sub.16 H.sub.13 I.sub.2 N.sub.3 O.sub.3.HCl requires: C, 32.82; H, 2.39; N, 7.18%.

Detailed Description Text (132):

4-(3'-Chloro-6'-hydroxylphenyl)amino-6,7-dimethoxyquinazoline(HI-P93) yield 93.08%; m.p.295.0.degree. C.(dec)..sup.- H NMR-DMSO-.sub.6 : .delta. 10.14(s, 1H, -NH), 9.16(s, 1H, --OH), 8.37(s, 1H, 2-h), 7.78(s, 2H, 5H), 7.57(d, 1H, J.sub.2',2' =2.4Hz, 2'-H),), 7.16(s, 1H, 8-H ), 7.07(dd, 1 H, J.sub.2',4' =2.4 Hz, J.sub.4',5' =8.7 Hz, 4'-H), 6.92(d, 1H, J.sub.4',5' -8.7 Hz, 5'-H), 3.93(s,3H, --OCH.sub.3). 3.92(s,3H, --OCH.sub.3). UV(MeOH): 205, 229.0, 251.0, 320.0 nm. IR (KBr).nu..sub.max : 3500(br), 3430, 2835, 1622, 1512, 1432, 1259 cm.sup.-1. GC/MS m/z 333(M.sup.- =2,13.41), 332(M.sup.- =1,9.73), 331(M.sup.+,39.47), 314 (M.sup.+,100.00). 298(7.64). Found: C, 52.25; H, 4.07; N, 11.39, C.sub.16 H.sub.14 ClN.sub.3 O.sub.3, HCl requires: C, 52.32; H, 4.09; N, 11.44%.

Detailed Description Text (133):

4-(3',5'-Dibromo-4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline-((HI -P97) . Yield 72.80%; m.p.>300.0.degree. C. .sup.1 H NMR(DMSO-d.sub.6): .delta. 9.71(s, 1H, --NH), 9.39(s, 1H, --OH), 8.48(s, OH, 2-h), 8.07(s, 2H, 2',6'-H), 7.76(s, 1H, 5-H), 7.17(s, 2H, 8-H), 3.94(s, 3H, --OCH.sub.3), 3.91(s, 3H, --OCH.sub.3). UV(MeOH): 208.0, 210.0, 245.0, 320.0 nm; IR(KBr).nu..sub.max : 3504(br), 3419, 2868, 1627, 1512, 1425, 1250, 1155 cm.sup.-1 ; GC/MS m/z 456(M.sup.1 =1, 54.40), 455(M.sup.-, 100.00), 454(M.sup.- 1, 78.01), 439(M.sup.- --OH, 7.96), 376(M.sup.- +1-Br, 9.76), 375(M.sup.- Br, 1091), 360(5.23). Anal. (C.sub.16 H.sub.13 Br.sub.2 N.sub.3 O.sub.3) C, H, N.

Detailed Description Text (134):

4-(4'-Hydroxylphenyl)-amino-6,7-dimethoxyquinazoline(HI-P131): yield 84.29%; m.p. 245.0-248.0.degree. C. IR(KBr).nu..sub.max : 3428, 2836, 1635, 1516, 1443, 1234 cm: .sup.1 H NMR(DMSO-d.sub.6 : .delta. 11.21 (s, 1H, --NH), 9.70(s, 1H, --OH), 8.74(s, 1H, 2-h), 8.22(s, 1H, 5-h), 7.40(d, 2H, J-8.9 Hz, 2',6'-H), 7.29(s, 1H, 8-H), 6.85 (d, 2H, J=8.9 Hz, 3',5'-H), 3.98(s, 3H, --OCH.sub.3, 3.97(s, 3H, --OCH.sub.2). GC/MS m/z 298 (M.sup.- =1, 100.00), 297(M.sup.-, 26.6), 296(M.sup.+ -1, 12.5). Anal. (C.sub.16,H.sub.15 N.sub.3 O.sub.3 HCl) Cl, H, N.

Detailed Description Text (135):

4-(2-Hydroxylphenyl)-amino-6,7-dimethoxyquinazoline(HI-P132): yield 82.49%; m.p. 255.0-258.0.degree. C. IR(KBr).nu..sub.max : 3500 (br), 3425, 2833, 1625, 1512, 1456, 1251, 1068 cm.sup.-1. .sup.1 H NMR(DMSO-d.sub.6): .delta. 9.78(s, 1H, --NH), 9.29(s, 1H, --OH), 8.33(s, 1H, 2-h), 7.85(s, 1H, 5-H), 7.41-6.83(m, 4H, 3',4',5',6'-H), 7.16(s, 1H, 8-H), 3.93(s, 3H, --OCH.sub.3, 3.92(s, 3H, --



OCH.sub.3), 280(M.sup.+ --OH, 10.0). Anal. (C.sub.16 H.sub.15 N.sub.3 O.sub.3, HCl) C, H, N.

Detailed Description Text (138):

4-(3'-Bromo-4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline(HI-P154) ; yield 89.90%; m.p.233.0-233.5.degree. C. .sup.1 H NMR(DMSO-d.sub.6): 10.08(s, 1h, --NH), 9.38(s, 1H, --OH), 8.40(s, 1H 2-H), 7.89(d, 1H, J.sub.2',6' =2.7 Hz, 2'-H), 7.75(s, 1H, 5-h), 7.55(dd, 1H, J.sub.5',6' =9.0 Hz, J.sub.2',6' =2.7 Hz, 6'-H), 7.14(s, 1H, 8-H), 6.97(d, 1H, J.sub.5',6' =9.0 Hz, 5'-H), 3.92(s, 3H, --OCH.sub.3), 3.90(s, 3H, --OCH.sub.3). UV(MeOH): 203.0, 222.0, 25.0, 335.0 nm. IR (KBr).nu..sub.max.sub..sub.- : 3431(br), 2841, 1624, 1498, 1423, 1244 cm.sup.-1. GC/MS m/z 378(M.sup.+ =2,90.68), 377(M.sup.+ =1, 37.49), 376(M.sup.+ , 100.00), 360 (MK.sup.+ , 3.63), 298(28.86), 282 (6.65). Anal. (C.sub.16 H.sub.14 BrN.sub.3 O.sub.3,HCl) C, H, N.

Detailed Description Text (154):

4-(4'-Hydroxyl-2'-chlorophenyl)-amino-6,7-dimethoxy-quinazoline(HI-P28 78) Yield 81.44%; m.p. 245.0-247.0.degree. C. .sup.1 H NMR(DMSO-d.sub.6): .delta. 11.39(s, 1H, --NH)O, 10.30(s, 1H, --OH), 8.75(s, 1H, 2-H), 8.24(s, 1H, 5-H), 7.38-6.85(m, 3H, 3',5',6'-H), 7.37(s, 1H, 8H), 3.98(s, 3H, --OCH.sub.3), 3.96(s, H3, --OCH.sub.3). UV(MeOH): 222.0, 234.0, 239.0, 245.0, 254.0 348.0 nm. (R (KBr).nu..sub.max : 3448, 3242, 3144, 3025, 2917, 2834, 1638, 1591, 1514, 1437, 1365, 1277, 1209 cm.sup.-1. GC/MS m/z: 332(M.sup.- +1, 5.00), 331(M, 17.00), 330 (M.sup.- -1, 5.00), 297(17.00), 296(100.00), 281(18.00), 280o(29.00), 253(9.00).

Detailed Description Text (157):

4-(4'-Hydroxy-3,5-diiodophenyl)-amino-6,7-dimethoxy-quinazoline(HI-P29 4) Yield 77.47%; m.p. 259.0-260.0.degree. C. .sup.1 H NMR(DMSO-d.sub.6): .delta. 11.13(s, 1H, NH), 9.73(s, 1H, --OH), 8.87(s, 1H, 2-H), 8.16(s, 1H, 5-H), 8.09(s, 2H, 1',6'-H), 7.28(s, 1H, 8H), 3.98(s, 6H, --OCH.sub.3). UV(MeOH).lambda..sub.max): 217.0, 227.0, 252.00 nm. IR(KBr.nu..sub.max : 3457, 3201, 2934, 2832, 2566, 1629, 1562, 1521, 1439, 1275, 1075 cm.sup.-1. GC/MS m/z: GC/MS m/z 422(M.sup.-I. 33.53), 405 (7.50), 281(86.67), 221(51.80), 207(91.30). Found: C, 32.60; H, 2.50; N, 6.92. C.sub.16 H.sub.13 I.sub.2 N.sub.3 O.sub.3.HCl requires: C. 32/82.'J. 2.39; N, 7.18%.

Detailed Description Text (160):

Fluorine Substituted Quinazoline Compounds

Detailed Description Text (161):

Fluorine substituted quinazoline derivatives were synthesized and characterized as discussed above for Example 1. The structures and physical data are shown below:

Detailed Description Text (180):

4-(4'-Hydroxyl-3',5'-difluorophenyl)-amino-6,7-dimethoxy-quinazoline (HI-P408) Yield. 83.15%, m.p.228.0-230.0 0.degree. C. .sup.1 H NMR(DMSO-d.sub.6): .delta. 11.46(s. 1H, --NH), 10.39(s. 1H, 2-H), 8.36(s. 1H, 5-H). 7.56, 7.54 (s. s. 2H. 2',6'-H), 7.33(s. 1H. 8-H), 4.00)s. 3H, --OCH.sub.3), 3.98(s. 3H, --OCH.sub.3). .sup.19 F NMR(DMSO-d.sub.6 : .delta.60.25, 60.22. Found: C, 52.04; H, 4.17; N, 11.10. C.sub.16 H.sub.13 F.sub.2 N.sub.3 O.sub.3.HCl. requires C, 52.03; H, 3.79;N, 11.38%.

Detailed Description Text (182):

Anti-Tumor Activities of Specific Quinazoline Compounds

Detailed Description Text (183):

The cytotoxicity of the substituted quinazoline derivative compounds against a variety of human tumor cells was evaluated. The relative importance of particular substituent groups on the compounds was also studied. The substituted quinazoline derivative compounds, prepared as described above, were tested, along with DMSO as

a control.

Detailed Description Text (185):

The cytotoxicity assay of various compounds against human tumor cell lines was performed using the MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide) assay (Boehringer Mannheim Corp., Indianapolis, Ind.). Briefly, exponentially growing tumor cells were seeded into a 96-well plate at a density of 2.5.times.10 cells/well and incubated for 36 hours at 37.degree. C. prior to drug exposure. On the day of treatment, culture medium was carefully aspirated from the wells and replaced with fresh medium containing the quinazoline compounds at concentrations ranging from 0.1 to 250 .mu.M. Triplicate wells were used for each treatment.

Detailed Description Text (205):

Antitumor Activity of Quinazolines In vivo

Detailed Description Text (206):

To test the anti-tumor activity of quinazolines in vivo, cancer cells were implanted and grown in mice in the presence of quinazoline.

Detailed Description Text (209):

The data are shown in FIG. 10A, and demonstrate that treatment of animals with the quinazolines of the invention (HI-P353 and HI-P364) inhibited the growth of breast cancer cell tumors as compared with untreated controls.

Detailed Description Text (212):

The data are shown in FIG. 10B and demonstrate that treatment of animals with the quinazolines of the invention (HI-P353 and HI-P364) inhibited the growth of brain tumors as compared with untreated controls.

Detailed Description Text (214):

The anti-tumor activity of the quinazolines of the invention was also studied with intracranial tumors. Nude mice were first anesthetized with Avertin. Under aseptic conditions in a laminar flow hood, a small hole was drilled at 2 mm to the right of the midline and 2 mm posterior to the bregma. An amount of 4.times.10.sup.5 U87 glioblastoma cells in 10 .mu.L of PBS were intracranially implanted using a Hamilton syringe into the right cerebral hemisphere of mice and a stereotaxic apparatus according to the method described in Huang, H. J. S. et al., J. Biol. Chem. 272:2927-2935, 1997.

Detailed Description Text (216):

FIG. 10C shows the survival rate of mice inflicted with intracranial tumors. Treatment of mice with quinazolines (HI-P353 and HI-P364) resulted in prolonged survival as compared with mice treated with vehicle alone.

Detailed Description Paragraph Table (1):

Bromine Substituted Quinazoline Compounds No Name Structure Formula MW 1 P-79  
 ##STR6## C.sub.16 H.sub.14 BrN.sub.3 O.sub.2 360 2 P-88 ##STR7## C.sub.17 H.sub.14  
 BrN.sub.3 O.sub.4 404 3 P-97 ##STR8## C.sub.16 H.sub.13 Br.sub.2 N.sub.3 O.sub.3  
 455 4 P-111 ##STR9## C.sub.17 H.sub.16 BrN.sub.3 O.sub.2 374 5 P-112 ##STR10##  
 C.sub.16 H.sub.13 Br.sub.2 N.sub.3 O.sub.2 439 6 P-154 ##STR11## C.sub.16 H.sub.14  
 BrN.sub.3 O.sub.3 376 7 P-160 ##STR12## C.sub.23 H.sub.18 BrN.sub.3 O.sub.2 448 8  
 P-164 ##STR13## C.sub.17 H.sub.13 BrN.sub.3 O.sub.3 373 9 P-190 ##STR14## C.sub.17  
 H.sub.16 BrN.sub.3 O.sub.3 389 10 P-210 ##STR15## C.sub.17 H.sub.15 Br.sub.2  
 N.sub.3 O.sub.2 453 11 P-211 ##STR16## C.sub.17 H.sub.15 Br.sub.2 N.sub.3 O.sub.2  
 453 12 P-212 ##STR17## C.sub.17 H.sub.15 Br.sub.2 N.sub.3 O.sub.2 453 13 P-214  
 ##STR18## C.sub.16 H.sub.13 BrFN.sub.3 O.sub.2 378 14 P-222 ##STR19## C.sub.16  
 H.sub.12 Br.sub.3 N.sub.3 O.sub.2 518 15 P-234 ##STR20## C.sub.17 H.sub.17 N.sub.3  
 O.sub.2 295 16 P-241 ##STR21## C.sub.17 H.sub.15 Br.sub.2 N.sub.3 O.sub.2 453 17 P-  
 258 ##STR22## C.sub.16 H.sub.15 N.sub.3 O.sub.2 281 18 P-260 ##STR23## C.sub.16

H.sub.14 BrN.sub.3 O.sub.2 360 19 P-261 ##STR24## C.sub.16 H.sub.14 BrN.sub.3  
 O.sub.2 360 20 P-262 ##STR25## C.sub.16 H.sub.13 Br.sub.2 N.sub.3 O.sub.2 439 21 P-  
 263 ##STR26## C.sub.16 H.sub.13 Br.sub.2 N.sub.3 O.sub.2 439

Detailed Description Paragraph Table (7):

TABLE 1 Cytotoxic Activity of Bromo Substituted Quinazoline Compounds against  
 Leukemic (NALM-6 & MOLT-3) and Breast Cancer (BT-20) NALM-6 MOLT-3 BT20 IC50 IC50  
 IC50 Drug (.mu.M) (.mu.M) (.mu.M) HI-P79 142.1 194.9 201.5 HI-P88 >250 >250 >250  
 HI-P97 >250 >250 26.1 HI-P111 200.6 >250 >250 HI-P154 12.5 9.1 >250 HI-P160 135.2  
 240.7 25.5 HI-P164 >250 >250 39.2 HI-P190 >250 >250 >250 HI-P210 >250 >250 >250 HI-  
 P211 >250 >250 >250 HI-P212 52.7 54.5 >250 HI-P214 >250 >250 >250 HI-P222 34.0 48.3  
 >250 HI-P234 >250 >250 >250 HI-P241 >250 >250 >250 HI-P258 >250 >250 >250 HI-P260  
 32.4 51.3 82.1 HI-P261 72.6 148.5 218.6 HI-P262 >250 >250 >250

Detailed Description Paragraph Table (8):

TABLE 2 Cytotoxic Activity of Chloro Substituted Quinazoline Compounds against  
 Leukemic (NALM-6 & MOLT-3) and Breast Cancer (BT-20) NALM-6 MOLT-3 BT20 IC50 IC50  
 IC50 Drug (.mu.m) (.mu.m) (.mu.m) HI-P87 95.9 >104.6 >250 HI-P93 >250 >250 >250 HI-  
 P189 >250 >250 >250 HI-P197 39.3 68.0 136.9 HI-P239 29.6 28.7 25.7 HI-P246 >250  
 >250 >250 HI-P268 215.2 227.4 121.5 HI-P269 >250 >250 >250 HI-P415 67.9 >250 38.1

Detailed Description Paragraph Table (9):

TABLE 2 Cytotoxic Activity of Chloro Substituted Quinazoline Compounds against  
 Leukemic (NALM-6 & MOLT-3) and Breast Cancer (BT-20) NALM-6 MOLT-3 BT20 IC50 IC50  
 IC50 Drug (.mu.m) (.mu.m) (.mu.m) HI-P87 95.9 >104.6 >250 HI-P93 >250 >250 >250 HI-  
 P189 >250 >250 >250 HI-P197 39.3 68.0 136.9 HI-P239 29.6 28.7 25.7 HI-P246 >250  
 >250 >250 HI-P268 215.2 227.4 121.5 HI-P269 >250 >250 >250 HI-P415 67.9 >250 38.1

Other Reference Publication (4):

Budesinsky, Z. et al., "A New Synthesis of the Quinazoline Nucleus", Collection of  
 Czechoslovak Chemical Communications, vol. 37, No. 8, pp. 2779-2785 (Aug. 1972).

Other Reference Publication (8):

Higashino, T. et al., "Reactions of the anion of quinazoline Reissert compound (3-  
 benzoyl-3, 4-dihydro-4-quinazolinecarbon itrile) with electrophiles", Chemical &  
 Pharmaceutical Bulletin, vol. 33, No. 3, pp. 950-961 (Mar. 1985).

Other Reference Publication (14):

Miyashita, A. et al., "An Approach to the Synthesis of a Papaverine Analogue  
 Containing a Quinazoline Ring System," Heterocycles, vol. 40, No. 2 pp. 653-660  
 (1995).

Other Reference Publication (16):

Myers, M. R. et al., "The Preparation and SAR of 4-(Anilino), 4-(Phenoxy), and 4-  
 (Thiopenoxy)-Quinazolines: Inhibitors of p56.sup.lck and EGF-R Tyrosine Kinase  
 Activity," Bioorganic & Medicinal Chemistry Letters, vol. 7, No. 4, pp. 417-420  
 (1997).

Other Reference Publication (17):

Narla, R. K. et al., "4-(3'-Bromo-4' hydroxylphenyl)-amino-6,7-  
 dimethoxyquinazoline: A Novel Quinazoline Derivative with Potent Cytotoxic Activity  
 against Human Glioblastoma Cells," Clinical Cancer Research, vol. 4, pp. 1405-1414  
 (Jun. 1998).

Other Reference Publication (18):

Narla, R. K. et al., Inhibition of Human Glioblastoma Cell Adhesion and Invasion by  
 4-(4'-Hydroxylphenyl)-amino-6,7-dimethoxyquinazoline (WHI-P131) and 4-(3'-Bromo-4'-  
hydroxylphenyl)-amino-6,7-dimethoxyquinazoline (WHI-P154), Clinical Cancer  
 Research, vol. 4, No. 10, pp. 2463-2471 (Oct. 1998).

Other Reference Publication (19):

Nomoto, Y. et al., "Studies on Cardiotonic Agents. I. Synthesis of Some Quinazoline Derivatives," Chem. Pharm. Bull., vol. 38, No. 6, pp. 1591-1595 (1990).

## Refine Search

### Search Results -

Terms	Documents
human and L7	67903

Database:

US Pre-Grant Publication Full-Text Database  
 US Patents Full-Text Database  
 US OCR Full-Text Database  
 EPO Abstracts Database  
 JPO Abstracts Database  
 Derwent World Patents Index  
 IBM Technical Disclosure Bulletins

Search:

L8



Refine Search

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### Search History

DATE: Monday, January 26, 2004    [Printable Copy](#)    [Create Case](#)

#### Set Name Query

side by side

#### Hit Count Set Name

result set

DB=USPT; PLUR=YES; OP=OR

<u>L8</u>	human and l7	67903	<u>L8</u>
<u>L7</u>	l6 and in vivo	82645	<u>L7</u>
<u>L6</u>	l3 and in vivo	82645	<u>L6</u>
<u>L5</u>	l3 and hydroxylphenyl	18	<u>L5</u>
<u>L4</u>	hydorxylphenyl and L3	0	<u>L4</u>
<u>L3</u>	L2 and dimethoxy	1056	<u>L3</u>
<u>L2</u>	quinazoline	4397	<u>L2</u>
<u>L1</u>	bromo-hydroxylphenyl-amino-dimethoxyquinazoline	0	<u>L1</u>

END OF SEARCH HISTORY

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present  
NEWS 4 DEC 08 INPADOC: Legal Status data reloaded  
NEWS 5 SEP 29 DISSABS now available on STN  
NEWS 6 OCT 10 PCTFULL: Two new display fields added  
NEWS 7 OCT 21 BIOSIS file reloaded and enhanced  
NEWS 8 OCT 28 BIOSIS file segment of TOXCENTER reloaded and enhanced  
NEWS 9 NOV 24 MSDS-CCOHS file reloaded  
NEWS 10 DEC 08 CABA reloaded with left truncation  
NEWS 11 DEC 08 IMS file names changed  
NEWS 12 DEC 09 Experimental property data collected by CAS now available  
in REGISTRY  
NEWS 13 DEC 09 STN Entry Date available for display in REGISTRY and CA/CAPplus  
NEWS 14 DEC 17 DGENE: Two new display fields added  
NEWS 15 DEC 18 BIOTECHNO no longer updated  
NEWS 16 DEC 19 CROPU no longer updated; subscriber discount no longer  
available  
NEWS 17 DEC 22 Additional INPI reactions and pre-1907 documents added to CAS  
databases  
NEWS 18 DEC 22 IFIPAT/IFIUDB/IFICDB reloaded with new data and search fields  
NEWS 19 DEC 22 ABI-INFORM now available on STN  
  
NEWS EXPRESS DECEMBER 28 CURRENT WINDOWS VERSION IS V7.00, CURRENT  
MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP),  
AND CURRENT DISCOVER FILE IS DATED 23 SEPTEMBER 2003  
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=> file medline

COST IN U.S. DOLLARS

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SESSION

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FILE 'MEDLINE' ENTERED AT 15:05:14 ON 26 JAN 2004

FILE LAST UPDATED: 24 JAN 2004 (20040124/UP). FILE COVERS 1958 TO DATE.

On December 14, 2003, the 2004 MeSH terms were loaded. See HELP RLOAD for details.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2004 vocabulary. See <http://www.nlm.nih.gov/mesh/> and [http://www.nih.gov/pubs/yechnbull/nd03/nd03\\_mesh.html](http://www.nih.gov/pubs/yechnbull/nd03/nd03_mesh.html) for a description on changes.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s c-jun inhibition

815633 C

11663 JUN

377377 INHIBITION

L1

2 C-JUN INHIBITION

(C(W)JUN(W)INHIBITION)

=> d l1 ti abs ibib tot

L1 ANSWER 1 OF 2 MEDLINE on STN

TI Dual-specificity protein tyrosine phosphatase VHR down-regulates c-Jun N-terminal kinase (JNK).

AB The JNK group (for c-Jun N-terminal kinase) of mitogen-activated protein kinases (MAP kinases) is activated in cells in response to environmental stress and cytokines. Activation of JNK is the result of dual phosphorylation by specific upstream kinases which phosphorylate the TxY motif. Much less is known concerning the down-regulation by protein phosphatases. Here, we demonstrate that the tyrosine-specific and constitutively-expressed phosphatase VHR (for VHL-Related) down-regulates the JNK signaling pathway at the level of JNK dephosphorylation. VHR was shown to efficiently dephosphorylate JNK and to form a tight complex with activated JNK when the catalytically-inactive C124S VHR mutant was employed as an in vivo substrate trap. Utilizing an in vitro assay, the transcription factor c-Jun specifically inhibited the ability of VHR to dephosphorylate JNK, likely by sterically blocking access to the phosphorylation sites when JNK and c-Jun form a complex. c-Jun has no effect on the ability of VHR to inactivate the ERK MAP kinases or to hydrolyze artificial substrates. The c-Jun inhibition results are discussed in terms of the resistant-nature of JNK dephosphorylation in cellular extracts and in terms of a general model in which VHR may be a general MAP kinase phosphatase whose specificity and activity are dictated by the presence of MAP kinase-associated proteins that inhibit dephosphorylation.

ACCESSION NUMBER: 2002230942 MEDLINE

DOCUMENT NUMBER: 21966460 PubMed ID: 11971192

TITLE: Dual-specificity protein tyrosine phosphatase VHR down-regulates c-Jun N-terminal kinase (JNK).

AUTHOR: Todd Jacob L; Rigas Johanna D; Rafty Louise A; Denu John M  
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, Oregon Health Sciences University, Portland, Oregon, OR 97201-3098, USA.

CONTRACT NUMBER: GM 59785 (NIGMS)

SOURCE: ONCOGENE, (2002 Apr 11) 21 (16) 2573-83.

Journal code: 8711562. ISSN: 0950-9232.

PUB. COUNTRY: England: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200205  
ENTRY DATE: Entered STN: 20020424  
Last Updated on STN: 20020509  
Entered Medline: 20020508

L1 ANSWER 2 OF 2 MEDLINE on STN

TI Regulation of mouse SP-B gene promoter by AP-1 family members.

AB The regulatory role of activator protein-1 (AP-1) family members in mouse surfactant protein (SP) B (mSP-B) promoter function was assessed in the mouse lung epithelial cell line MLE-15. Expression of recombinant Jun B and c-Jun inhibited mSP-B promoter activity by 50-75%. Although c-Fos expression did not alter mSP-B transcription, Jun D enhanced mSP-B promoter activity and reversed inhibition of mSP-B by c-Jun or Jun B. A proximal AP-1 binding site (-18 to -10 bp) was identified that overlaps a thyroid transcription factor-1 binding site. Mutation of this proximal AP-1 site blocked both Jun B inhibition and Jun D enhancement and partially blocked c-Jun inhibition of promoter activity. Promoter deletion mutants were used to identify additional sequences mediating the inhibitory effects of c-Jun in the distal region from -397 to -253 bp. The AP-1 element in this distal site (-370 to -364 bp) is part of a composite binding site wherein AP-1, cAMP response element binding protein, thyroid transcription factor-1, and nuclear factor I interact. Point mutation of the distal AP-1 binding site partially blocked c-Jun-mediated inhibition of the SP-B promoter. Both stimulatory (Jun D) and inhibitory (c-Jun/Jun B) effects of AP-1 family members on mSP-B promoter activity are mediated by distinct cis-acting elements in the mSP-B 5'-flanking region.

ACCESSION NUMBER: 1999345730 MEDLINE

DOCUMENT NUMBER: 99345730 PubMed ID: 10409233

TITLE: Regulation of mouse SP-B gene promoter by AP-1 family members.

AUTHOR: Sever-Chroneos Z; Bachurski C J; Yan C; Whitsett J A

CORPORATE SOURCE: Division of Pulmonary Biology, Children's Hospital Medical Center, Cincinnati, Ohio 45229, USA.

CONTRACT NUMBER: HL-38859 (NHLBI)

HL-56387 (NHLBI)

HL-60907 (NHLBI)

SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY, (1999 Jul) 277 (1 Pt 1) L79-88.

Journal code: 0370511. ISSN: 0002-9513.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199908

ENTRY DATE: Entered STN: 19990827

Last Updated on STN: 19990827

Entered Medline: 19990818



## Refine Search

### Search Results -

Terms	Documents
L3 and hydroxylphenyl	28

Database:

US Pre-Grant Publication Full-Text Database  
 US Patents Full-Text Database  
 US OCR Full-Text Database  
 EPO Abstracts Database  
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 Derwent World Patents Index  
 IBM Technical Disclosure Bulletins

Search:

L4





### Search History

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#### Set Name Query

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result set

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<u>L4</u>	L3 and hydroxylphenyl	28	<u>L4</u>
<u>L3</u>	L2 and I1	155	<u>L3</u>
<u>L2</u>	dimethoxyquinazoline	268	<u>L2</u>
<u>L1</u>	inhibit c-jun activation	370075	<u>L1</u>

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## Hit List

Clear	Generate Collection	Print	Fwd Refs	Bkwd Refs
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Search Results - Record(s) 1 through 10 of 28 returned.

☐ 1. Document ID: US 6638939 B2

L4: Entry 1 of 28

File: USPT

Oct 28, 2003

US-PAT-NO: 6638939

DOCUMENT-IDENTIFIER: US 6638939 B2

TITLE: 6,7-dimethoxyquinazolines and therapeutic use thereof

DATE-ISSUED: October 28, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Liu; Xing-Ping	Minneapolis	MN		
Narla; Rama Krishna	St. Paul	MN		

US-CL-CURRENT: 514/266.4; 544/293

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequence	Attachment	Claims	KIMC	Draw. De
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☐ 2. Document ID: US 6627655 B2

L4: Entry 2 of 28

File: USPT

Sep 30, 2003

US-PAT-NO: 6627655

DOCUMENT-IDENTIFIER: US 6627655 B2

TITLE: Vanadium (IV) metallocene complexes having spermicidal activity

DATE-ISSUED: September 30, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
D'Cruz; Osmond	Maplewood	MN		
Ghosh; Phalguni	St. Anthony	MN		
Uckun; Fatih M.	White Bear Lake	MN		

US-CL-CURRENT: 514/492; 556/43

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWIC	Draw D
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☐ 3. Document ID: US 6592845 B2

L4: Entry 3 of 28

File: USPT

Jul 15, 2003

US-PAT-NO: 6592845

DOCUMENT-IDENTIFIER: US 6592845 B2

TITLE: Estrogens for treating ALS

DATE-ISSUED: July 15, 2003

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Trieu; Vuoung N.	Roseville	MN		
Liu; Xing-Ping	Minneapolis	MN		

US-CL-CURRENT: 424/9.1; 424/1.11, 424/9.2, 549/273

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWIC	Draw D
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☐ 4. Document ID: US 6552027 B2

L4: Entry 4 of 28

File: USPT

Apr 22, 2003

US-PAT-NO: 6552027

DOCUMENT-IDENTIFIER: US 6552027 B2

TITLE: Quinazolines for treating brain tumor

DATE-ISSUED: April 22, 2003

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Narla; Rama Krishna	St. Paul	MN		
Liu; Xing-Ping	Minneapolis	MN		

US-CL-CURRENT: 514/266.4

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWIC	Draw D
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☐ 5. Document ID: US 6500860 B2

L4: Entry 5 of 28

File: USPT

Dec 31, 2002

US-PAT-NO: 6500860

h e b b g e e f e h e f b e

DOCUMENT-IDENTIFIER: US 6500860 B2

**\*\* See image for Certificate of Correction \*\***

TITLE: Vanadium (IV) metallocene complexes having spermicidal activity

DATE-ISSUED: December 31, 2002

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
D'Cruz; Osmond	Maplewood	MN		
Ghosh; Phalguni	St. Anthony	MN		
Uckun; Fatih M.	White Bear Lake	MN		

US-CL-CURRENT: 514/492

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	RWMC	Draw De
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☐ 6. Document ID: US 6495556 B2

L4: Entry 6 of 28

File: USPT

Dec 17, 2002

US-PAT-NO: 6495556

DOCUMENT-IDENTIFIER: US 6495556 B2

**\*\* See image for Certificate of Correction \*\***

TITLE: Dimethoxy quinazolines for treating diabetes

DATE-ISSUED: December 17, 2002

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Leak	MN		
Sudbeck; Elise A.	St. Paul	MN		
Cetkovic; Marina	Maplewood	MN		
Malaviya; Ravi	Shoreview	MN		
Liu; Xing-Ping	Minneapolis	MN		

US-CL-CURRENT: 514/266.4

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	RWMC	Draw De
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☐ 7. Document ID: US 6469013 B2

L4: Entry 7 of 28

File: USPT

Oct 22, 2002

US-PAT-NO: 6469013

DOCUMENT-IDENTIFIER: US 6469013 B2

**\*\* See image for Certificate of Correction \*\***

TITLE: Therapeutic compounds

DATE-ISSUED: October 22, 2002

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Sudbeck; Elise A.	St. Paul	MN		
Cetkovic; Marina	Maplewood	MN		
Malaviya; Ravi	Shoreview	MN		
Liu; Xing-Ping	Minneapolis	MN		

US-CL-CURRENT: 514/266.3; 514/266.4

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWC	Drawings
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☐ 8. Document ID: US 6452005 B1

L4: Entry 8 of 28

File: USPT

Sep 17, 2002

US-PAT-NO: 6452005

DOCUMENT-IDENTIFIER: US 6452005 B1

**\*\* See image for Certificate of Correction \*\***

TITLE: JAK-3 inhibitors for treating allergic disorders

DATE-ISSUED: September 17, 2002

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Malaviya; Ravi	Shoreview	MN		
Sudbeck; Elise A.	St. Paul	MN		

US-CL-CURRENT: 544/293

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWC	Drawings
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☐ 9. Document ID: US 6432941 B1

L4: Entry 9 of 28

File: USPT

Aug 13, 2002

US-PAT-NO: 6432941

DOCUMENT-IDENTIFIER: US 6432941 B1

TITLE: Vanadium compounds for treating cancer

DATE-ISSUED: August 13, 2002

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		

h e b b g e e f e h e f b e

Dong; Yanhong                      Moundsvew                      MN  
Gosh; Phalguni                      Shoreview                      MN

US-CL-CURRENT: 514/185; 514/184, 514/186, 514/187, 514/188, 514/492, 546/10, 546/2,  
546/6, 546/88, 549/206, 549/210, 549/212

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWIC	Draw D
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☐ 10. Document ID: US 6410545 B1

L4: Entry 10 of 28

File: USPT

Jun 25, 2002

US-PAT-NO: 6410545

DOCUMENT-IDENTIFIER: US 6410545 B1

**\*\* See image for Certificate of Correction \*\***

TITLE: Lipid lowering quinazoline dietary supplement composition

DATE-ISSUED: June 25, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Trieu; Vuong N.	Roseville	MN		
Liu; Xing-Ping	Minneapolis	MN		

US-CL-CURRENT: 514/266.1; 514/266.3

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWIC	Draw D
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Clear	Generate Collection	Print	Fwd Refs	Bkwd Refs	Generate OACS
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Terms	Documents
L3 and hydroxylphenyl	28

Display Format: CIT [Change Format](#)

[Previous Page](#)

[Next Page](#)

[Go to Doc#](#)

## Refine Search

### Search Results -

Terms	Documents
L6 and L4	15

Database:

US Pre-Grant Publication Full-Text Database  
 US Patents Full-Text Database  
 US OCR Full-Text Database  
 EPO Abstracts Database  
 JPO Abstracts Database  
 Derwent World Patents Index  
 IBM Technical Disclosure Bulletins

Search:

L7



Refine Search

Recall Text



Clear

Interrupt

### Search History

DATE: Monday, January 26, 2004    [Printable Copy](#)    [Create Case](#)

**Set Name Query**

side by side

**Hit Count Set Name**

result set

*DB=USPT; PLUR=YES; OP=OR*

<u>L7</u>	L6 and l4	15	<u>L7</u>
<u>L6</u>	c-jun activation adj2 inhibition	2036	<u>L6</u>
<u>L5</u>	L4 and inhibit c-jun	1002	<u>L5</u>
<u>L4</u>	L3 and hydroxylphenyl	28	<u>L4</u>
<u>L3</u>	L2 and l1	155	<u>L3</u>
<u>L2</u>	dimethoxyquinazoline	268	<u>L2</u>
<u>L1</u>	inhibit c-jun activation	370075	<u>L1</u>

END OF SEARCH HISTORY

## Hit List

Clear	Generate Collection	Print	Fwd Refs	Bkwd Refs
Generate OACS				

Search Results - Record(s) 1 through 10 of 15 returned.

☐ 1. Document ID: US 6638939 B2

L7: Entry 1 of 15

File: USPT

Oct 28, 2003

US-PAT-NO: 6638939

DOCUMENT-IDENTIFIER: US 6638939 B2

TITLE: 6,7-dimethoxyquinazolines and therapeutic use thereof

DATE-ISSUED: October 28, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Liu; Xing-Ping	Minneapolis	MN		
Narla; Rama Krishna	St. Paul	MN		

US-CL-CURRENT: 514/266.4; 544/293

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequence	Abstract	Claims	KMIC	Draw D
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☐ 2. Document ID: US 6552027 B2

L7: Entry 2 of 15

File: USPT

Apr 22, 2003

US-PAT-NO: 6552027

DOCUMENT-IDENTIFIER: US 6552027 B2

TITLE: Quinazolines for treating brain tumor

DATE-ISSUED: April 22, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Narla; Rama Krishna	St. Paul	MN		
Liu; Xing-Ping	Minneapolis	MN		

US-CL-CURRENT: 514/266.4



Full	Title	Citation	Front	Review	Classification	Date	Reference	Services	Drawings	Claims	KWIC	Draw D
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☐ 3. Document ID: US 6495556 B2

L7: Entry 3 of 15

File: USPT

Dec 17, 2002

US-PAT-NO: 6495556

DOCUMENT-IDENTIFIER: US 6495556 B2

**\*\* See image for Certificate of Correction \*\***

TITLE: Dimethoxy quinazolines for treating diabetes

DATE-ISSUED: December 17, 2002

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Leak	MN		
Sudbeck; Elise A.	St. Paul	MN		
Cetkovic; Marina	Maplewood	MN		
Malaviya; Ravi	Shoreview	MN		
Liu; Xing-Ping	Minneapolis	MN		

US-CL-CURRENT: 514/266.4

Full	Title	Citation	Front	Review	Classification	Date	Reference	Services	Drawings	Claims	KWIC	Draw D
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☐ 4. Document ID: US 6469013 B2

L7: Entry 4 of 15

File: USPT

Oct 22, 2002

US-PAT-NO: 6469013

DOCUMENT-IDENTIFIER: US 6469013 B2

**\*\* See image for Certificate of Correction \*\***

TITLE: Therapeutic compounds

DATE-ISSUED: October 22, 2002

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Sudbeck; Elise A.	St. Paul	MN		
Cetkovic; Marina	Maplewood	MN		
Malaviya; Ravi	Shoreview	MN		
Liu; Xing-Ping	Minneapolis	MN		

US-CL-CURRENT: 514/266.3; 514/266.4

Full	Title	Citation	Front	Review	Classification	Date	Reference	Services	Drawings	Claims	KWIC	Draw D
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☐ 5. Document ID: US 6452005 B1

L7: Entry 5 of 15

File: USPT

Sep 17, 2002

US-PAT-NO: 6452005

DOCUMENT-IDENTIFIER: US 6452005 B1

**\*\* See image for Certificate of Correction \*\***

TITLE: JAK-3 inhibitors for treating allergic disorders

DATE-ISSUED: September 17, 2002

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Malaviya; Ravi	Shoreview	MN		
Sudbeck; Elise A.	St. Paul	MN		

US-CL-CURRENT: 544/293

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequence	Attachments	Claims	KWIC	Draw D
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☐ 6. Document ID: US 6358962 B2

L7: Entry 6 of 15

File: USPT

Mar 19, 2002

US-PAT-NO: 6358962

DOCUMENT-IDENTIFIER: US 6358962 B2

TITLE: 6,7-Dimethoxyquinazolines and therapeutic use thereof

DATE-ISSUED: March 19, 2002

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Liu; Xing-Ping	Minneapolis	MN		
Narla; Rama Krishna	St. Paul	MN		

US-CL-CURRENT: 514/266.4; 544/283, 544/293

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequence	Attachments	Claims	KWIC	Draw D
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☐ 7. Document ID: US 6326373 B1

L7: Entry 7 of 15

File: USPT

Dec 4, 2001

US-PAT-NO: 6326373

DOCUMENT-IDENTIFIER: US 6326373 B1

**\*\* See image for Certificate of Correction \*\***

TITLE: JAK-3 inhibitors for treating allergic disorders

DATE-ISSUED: December 4, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Malavia; Ravi	Shoreview	MN		
Sudbeck; Elise A.	St. Paul	MN		

US-CL-CURRENT: 514/266.1; 514/266.3, 514/266.4

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWIC	Drawings
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☐ 8. Document ID: US 6316454 B1

L7: Entry 8 of 15

File: USPT

Nov 13, 2001

US-PAT-NO: 6316454

DOCUMENT-IDENTIFIER: US 6316454 B1

TITLE: 6,7-Dimethoxy-4-anilinoquinazolines

DATE-ISSUED: November 13, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Narla; Rama Krishna	St. Paul	MN		
Liu; Xing-Ping	Minneapolis	MN		

US-CL-CURRENT: 514/266.3; 514/266.4, 544/293

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWIC	Drawings
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☐ 9. Document ID: US 6313130 B1

L7: Entry 9 of 15

File: USPT

Nov 6, 2001

US-PAT-NO: 6313130

DOCUMENT-IDENTIFIER: US 6313130 B1

**\*\* See image for Certificate of Correction \*\***

TITLE: JAK-3 inhibitors for treating allergic disorders

DATE-ISSUED: November 6, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Malaviya; Ravi	Shoreview	MN		
Sudbeck; Elise A.	St. Paul	MN		

US-CL-CURRENT: [514/266.24](#); [514/266.3](#), [514/266.4](#), [514/267](#)

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequence	Attachments	Claims	RMIC	Draw D
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☐ 10. Document ID: US 6313129 B1

L7: Entry 10 of 15

File: USPT

Nov 6, 2001

US-PAT-NO: 6313129

DOCUMENT-IDENTIFIER: US 6313129 B1

TITLE: Therapeutic compounds

DATE-ISSUED: November 6, 2001

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Sudbeck; Elise A.	St. Paul	MN		
Cetkovic; Marina	Maplewood	MN		
Malaviya; Ravi	Shoreview	MN		
Liu; Xing-Ping	Minneapolis	MN		

US-CL-CURRENT: [514/266.3](#); [514/266.4](#)

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequence	Attachments	Claims	RMIC	Draw D
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Clear	Generate Collection	Print	Fwd Refs	Bkwd Refs	Generate OACS
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Terms	Documents
L6 and L4	15

Display Format:  [Previous Page](#)[Next Page](#)[Go to Doc#](#)

## Hit List

Clear	Generate Collection	Print	Fwd Refs	Bkwd Refs
Generate OACS				

Search Results - Record(s) 1 through 10 of 15 returned.

☐ 1. Document ID: US 6638939 B2

L7: Entry 1 of 15

File: USPT

Oct 28, 2003

US-PAT-NO: 6638939

DOCUMENT-IDENTIFIER: US 6638939 B2

TITLE: 6,7-dimethoxyquinazolines and therapeutic use thereof

DATE-ISSUED: October 28, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Liu; Xing-Ping	Minneapolis	MN		
Narla; Rama Krishna	St. Paul	MN		

US-CL-CURRENT: 514/266.4; 544/293

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequence	Attachment	Claims	KWIC	Drawings
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☐ 2. Document ID: US 6552027 B2

L7: Entry 2 of 15

File: USPT

Apr 22, 2003

US-PAT-NO: 6552027

DOCUMENT-IDENTIFIER: US 6552027 B2

TITLE: Quinazolines for treating brain tumor

DATE-ISSUED: April 22, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Narla; Rama Krishna	St. Paul	MN		
Liu; Xing-Ping	Minneapolis	MN		

US-CL-CURRENT: 514/266.4

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequence	Abstract	Claims	KWIC	Draw D
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☐ 3. Document ID: US 6495556 B2

L7: Entry 3 of 15

File: USPT

Dec 17, 2002

US-PAT-NO: 6495556

DOCUMENT-IDENTIFIER: US 6495556 B2

**\*\* See image for Certificate of Correction \*\***

TITLE: Dimethoxy quinazolines for treating diabetes

DATE-ISSUED: December 17, 2002

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Sudbeck; Elise A.	St. Paul	MN		
Cetkovic; Marina	Maplewood	MN		
Malaviya; Ravi	Shoreview	MN		
Liu; Xing-Ping	Minneapolis	MN		

US-CL-CURRENT: 514/266.4

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequence	Abstract	Claims	KWIC	Draw D
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☐ 4. Document ID: US 6469013 B2

L7: Entry 4 of 15

File: USPT

Oct 22, 2002

US-PAT-NO: 6469013

DOCUMENT-IDENTIFIER: US 6469013 B2

**\*\* See image for Certificate of Correction \*\***

TITLE: Therapeutic compounds

DATE-ISSUED: October 22, 2002

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Sudbeck; Elise A.	St. Paul	MN		
Cetkovic; Marina	Maplewood	MN		
Malaviya; Ravi	Shoreview	MN		
Liu; Xing-Ping	Minneapolis	MN		

US-CL-CURRENT: 514/266.3; 514/266.4

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequence	Abstract	Claims	KWIC	Draw D
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☐ 5. Document ID: US 6452005 B1

L7: Entry 5 of 15

File: USPT

Sep 17, 2002

US-PAT-NO: 6452005

DOCUMENT-IDENTIFIER: US 6452005 B1

**\*\* See image for Certificate of Correction \*\***

TITLE: JAK-3 inhibitors for treating allergic disorders

DATE-ISSUED: September 17, 2002

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Malaviya; Ravi	Shoreview	MN		
Sudbeck; Elise A.	St. Paul	MN		

US-CL-CURRENT: 544/293

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Abstracts	Claims	KWIC	Draw D
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☐ 6. Document ID: US 6358962 B2

L7: Entry 6 of 15

File: USPT

Mar 19, 2002

US-PAT-NO: 6358962

DOCUMENT-IDENTIFIER: US 6358962 B2

TITLE: 6,7-Dimethoxyquinazolines and therapeutic use thereof

DATE-ISSUED: March 19, 2002

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Liu; Xing-Ping	Minneapolis	MN		
Narla; Rama Krishna	St. Paul	MN		

US-CL-CURRENT: 514/266.4; 544/283, 544/293

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Abstracts	Claims	KWIC	Draw D
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☐ 7. Document ID: US 6326373 B1

L7: Entry 7 of 15

File: USPT

Dec 4, 2001

US-PAT-NO: 6326373

DOCUMENT-IDENTIFIER: US 6326373 B1

**\*\* See image for Certificate of Correction \*\***

TITLE: JAK-3 inhibitors for treating allergic disorders

DATE-ISSUED: December 4, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Malavia; Ravi	Shoreview	MN		
Sudbeck; Elise A.	St. Paul	MN		

US-CL-CURRENT: 514/266.1; 514/266.3, 514/266.4

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequence	Abstract	Claims	KWIC	Draw. De
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☐ 8. Document ID: US 6316454 B1

L7: Entry 8 of 15

File: USPT

Nov 13, 2001

US-PAT-NO: 6316454

DOCUMENT-IDENTIFIER: US 6316454 B1

TITLE: 6,7-Dimethoxy-4-anilinoquinazolines

DATE-ISSUED: November 13, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Narla; Rama Krishna	St. Paul	MN		
Liu; Xing-Ping	Minneapolis	MN		

US-CL-CURRENT: 514/266.3; 514/266.4, 544/293

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequence	Abstract	Claims	KWIC	Draw. De
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☐ 9. Document ID: US 6313130 B1

L7: Entry 9 of 15

File: USPT

Nov 6, 2001

US-PAT-NO: 6313130

DOCUMENT-IDENTIFIER: US 6313130 B1

**\*\* See image for Certificate of Correction \*\***

TITLE: JAK-3 inhibitors for treating allergic disorders

DATE-ISSUED: November 6, 2001

INVENTOR-INFORMATION:



NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Malaviya; Ravi	Shoreview	MN		
Sudbeck; Elise A.	St. Paul	MN		

US-CL-CURRENT: [514/266.24](#); [514/266.3](#), [514/266.4](#), [514/267](#)

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequence	Abstract	Claims	KWIC	Draw D
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☐ 10. Document ID: US 6313129 B1

L7: Entry 10 of 15

File: USPT

Nov 6, 2001

US-PAT-NO: 6313129

DOCUMENT-IDENTIFIER: US 6313129 B1

TITLE: Therapeutic compounds

DATE-ISSUED: November 6, 2001

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Sudbeck; Elise A.	St. Paul	MN		
Cetkovic; Marina	Maplewood	MN		
Malaviya; Ravi	Shoreview	MN		
Liu; Xing-Ping	Minneapolis	MN		

US-CL-CURRENT: [514/266.3](#); [514/266.4](#)

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequence	Abstract	Claims	KWIC	Draw D
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Clear	Generate Collection	Print	Fwd Refs	Bkwd Refs	Generate OACS
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Terms	Documents
L6 and L4	15

Display Format:  [Previous Page](#)[Next Page](#)[Go to Doc#](#)

## Hit List

Clear	Generate Collection	Print	Fwd Refs	Bkwd Refs
Generate OACS				

Search Results - Record(s) 11 through 15 of 15 returned.

☐ 11. Document ID: US 6258820 B1

L7: Entry 11 of 15

File: USPT

Jul 10, 2001

US-PAT-NO: 6258820

DOCUMENT-IDENTIFIER: US 6258820 B1

TITLE: Synthesis and anti-tumor activity of 6,7-dialkoxy-4-phenylamino-quinazolines

DATE-ISSUED: July 10, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Faith M.	White Bear Lake	MN		
Liu; Xing-Ping	Minneapolis	MN		
Narla; Rama Krishna	St. Paul	MN		

US-CL-CURRENT: 514/266.4; 544/293

Full	Title	Citation	Front	Review	Classification	Date	Reference	Searches	Abstracts	Claims	KMOC	Draw D
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☐ 12. Document ID: US 6177433 B1

L7: Entry 12 of 15

File: USPT

Jan 23, 2001

US-PAT-NO: 6177433

DOCUMENT-IDENTIFIER: US 6177433 B1

**\*\* See image for Certificate of Correction \*\***

TITLE: JAK-3 inhibitors for treating allergic disorders

DATE-ISSUED: January 23, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Malavia; Ravi	Shoreview	MN		
Sudbeck; Elise A.	St. Paul	MN		

US-CL-CURRENT: 514/266.4; 514/267

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequence	Attachments	Claims	KWC	Draw De
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☐ 13. Document ID: US 6080748 A

L7: Entry 13 of 15

File: USPT

Jun 27, 2000

US-PAT-NO: 6080748

DOCUMENT-IDENTIFIER: US 6080748 A

TITLE: Therapeutic use of JAK-3 inhibitors

DATE-ISSUED: June 27, 2000

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Malavia; Ravi	Shoreview	MN		
Sudbeck; Elise A.	St. Paul	MN		

US-CL-CURRENT: 424/178.1; 514/266.1, 514/266.3, 514/266.4

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequence	Attachments	Claims	KWC	Draw De
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☐ 14. Document ID: US 6080747 A

L7: Entry 14 of 15

File: USPT

Jun 27, 2000

US-PAT-NO: 6080747

DOCUMENT-IDENTIFIER: US 6080747 A

TITLE: JAK-3 inhibitors for treating allergic disorders

DATE-ISSUED: June 27, 2000

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Malavia; Ravi	Shoreview	MN		
Sudbeck; Elise A.	St. Paul	MN		

US-CL-CURRENT: 514/266.1; 514/266.3, 514/266.4

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequence	Attachments	Claims	KWC	Draw De
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☐ 15. Document ID: US 6066640 A

L7: Entry 15 of 15

File: USPT

May 23, 2000

US-PAT-NO: 6066640

DOCUMENT-IDENTIFIER: US 6066640 A

TITLE: Hydroxy-halo-quinazolines for augmentation of mast cell bactericidal activity

DATE-ISSUED: May 23, 2000

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Malaviya; Ravi	Shoreview	MN		

US-CL-CURRENT: 514/266.4; 514/267

Full	Title	Citation	Front	Review	Classification	Date	Reference	SEQUENCE	APPLICABLE	Claims	KWC	Draw D
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Terms	Documents
L6 and L4	15

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